

POTENTIAL FOR CARDIOVASCULAR EXERCISE DOSING TO IMPROVE
CARDIORESPIRATORY FITNESS IN BREAST CANCER SURVIVORS

BY

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Abstract

With an increase in early detection and curative treatment for breast cancer, there is a growing number of breast cancer survivors. Cancer survivors are at greater risk than their age matched peers for long-term health sequelae including recurrence of primary tumors and cardiovascular disease (CVD). Besides the direct effects of cancer treatment and a genetic predisposition, lifestyle factors are believed to contribute to these comorbid conditions. Despite knowing the benefits associated with an active lifestyle, breast cancer survivors have reported to decrease their activity level by as much as two hours or more per week, based on their treatment regimen. Guidelines for diet and/or exercise targeting cancer survivors have been proposed, but a paucity of data is available on optimal interventions for improving lifestyle behavior change in this population.

This dissertation was undertaken to address important unanswered questions. Specifically, can prescribed home-based exercise dosing be performed in a safe and effective manner during a combined diet and exercise intervention? And, will cardiovascular exercise dosing help improve selected outcomes of interest for breast cancer survivors?

Initially, we performed a cross-sectional study to investigate the cardiorespiratory fitness (VO_{2max}) level and body composition (weight, BMI, % body fat) in breast cancer survivors. We reported that breast cancer survivors had a low VO_{2max} compared to normal values in a healthy population. In addition, submaximal VO_2 exercise testing on a treadmill and elliptical trainer had a strong correlation to the gold standard test for measuring cardiorespiratory fitness on a treadmill.

Next, we undertook study to investigate the feasibility of using cardiovascular exercise dosing during a 17 week combined diet, home-based exercise, and behavior modification intervention. For simplicity, we will refer to this 17 week intervention as the “Energy Balance Program” throughout the remainder of this dissertation. In addition to investigating feasibility, we analyzed the potential for cardiovascular exercise dosing to have different effects on CVD and breast cancer risk factors including low VO_{2max} and weight gain during an Energy Balance Program. Nineteen female breast cancer survivors participated in an Energy Balance Program. One cohort received “usual care” cardiovascular exercise instructions including moderate continuous exercise (MCT) and a second cohort was prescribed cardiovascular exercise dosing in the form of interval training (IT). Both groups reported significant improvements in VO_{2max} and body composition. Additionally, the IT group had a significantly greater improvement in VO_{2max} compared to MCT, without any cardiovascular related adverse events (AE).

In conclusion, we were able to demonstrate a high correlation between sub-maximal and maximal exercise testing using both the treadmill and arc trainer in breast cancer survivors at high risk for CVD. In addition, breast cancer survivors in our study had a low VO_{2max} , but were able to successfully participate in a home based exercise and weight loss program, resulting in significant improvements in body composition and VO_{2max} , with significantly greater improvements in the IT versus MCT group for VO_{2max} .

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Chapter 1

Introduction

1.1 Overview

Approximately 227,000 women were estimated to be diagnosed with and over 39,510 deaths will be attributed to breast cancer in 2012 (ACS, 2012). Early detection and targeted therapy have resulted in a new chronic disease population in many developed countries (K. H. Schmitz, Stout, Andrews, Binkley, & Smith, 2012). Consequently, a trend towards a growing population of women surviving after diagnosis exceeds 2.5 million breast cancer survivors in the United States (ACS, 2012). Incidence rates for breast cancer in the United States remained constant between 1999 and 2008, but the death rates decreased for the same period (Eheman, et al., 2012). This decrease in breast cancer mortality was only seen in women older than 50, and may be influenced by a decline in the use of hormone therapy after menopause (ACS, 2012). Therefore, an increasing population of breast cancer survivors are faced with unique challenges including physiological and psychological sequelae as a result of the direct and indirect effects of their cancer treatment (Hewitt, Rowland, & Yancik, 2003).

The long-term effects of cancer treatment may lead to accelerated declines in physical function compared to those living without a history of cancer (K. H. Schmitz, Cappola, Stricker, Sweeney, & Norman, 2007). Greater than 75% of breast cancer survivors will live ten years after diagnosis, but suffer from late and long-term effects of breast cancer treatment on total body systems (NCI, SEER 1996-2007). Multiple physiological systems including cardiorespiratory and muscular endurance contribute to optimal physical function (Hewitt, et al., 2003; K. H. Schmitz, et al., 2007); and there is evidence that adjuvant therapy during breast cancer treatment can alter cardiorespiratory function. Studies have shown radiation therapy (Lind, et al., 1998; Ooi,

et al., 2001) and chemotherapy agents (Ng, Better, & Green, 2006; Theuws, et al., 1999) can be toxic to the heart and lungs, especially when used in combination (Shapiro, et al., 1998; Shapiro & Recht, 2001). Thus, the effects of breast cancer treatment can contribute to a diminished functional mobility mediated through the effects to the cardiorespiratory system.

Observational evidence from the Nurses' Health Study has described that breast cancer survivors experience long-term functional mobility (moderate and vigorous intensity activities) deficits, measured by self-reported survey (SF-36), when compared to women with no history of cancer (Michael, Kawachi, Berkman, Holmes, & Colditz, 2000). The decline in activity can be instrumental in both pre- and post-menopausal weight gain, which is common after a breast cancer diagnosis (Goodwin, et al., 2002; Vance, Mourtzakis, McCargar, & Hanning, 2011). The Annual Report to the Nation on the Status of cancer suggests that weight gain and insufficient activity contributes to the increased incidence of many cancers and adversely affects the quality of life in cancer survivors (Eheman, et al., 2012).

Recurrence of the primary malignancy and cardiac events are the leading causes of death in long-term cancer survivors, while the incidence of cardiac events and occurrence of breast cancer share common modifiable risk factors (Figure 1.1). Strategies for improving long-term health outcomes for the growing number of breast cancer survivors are important due to the increased prevalence of CVD and risk for recurrence of cancer. This dissertation begins by introducing an intervention model for targeting factors related to tumorigenesis and CVD in breast cancer survivors that display risk factors for both diseases. Figure 1.2 depicts the breast cancer survivor

disease prevention model. Two primary components of the model are: 1) identify those at risk due to targeted *modifiable risk factors*, and 2) determine an effective *intervention strategy* for decreasing CVD and recurrence risk. Studies suggest that combined diet and exercise interventions improve weight and physical activity as seen in Table 1.1 (Pekmezi & Demark-Wahnefried, 2011). A recent group home-based treatment delivery approach using combined diet and exercise reported significant improvements in weight loss and physical activity in breast cancer survivors (Befort, et al., 2012). Additionally, diet and physical activity guidelines targeting cancer survivors have been issued by the American Cancer Society (ACS) and American College of Sports Medicine (ACSM) (Doyle, et al., 2006; K. H. Schmitz, et al., 2010). However, more research is needed on different exercise prescriptions and their effect on targeted sustainable outcomes in breast cancer survivors.

Women Diagnosed with Breast Cancer: A Population Already at Risk for CVD

The Framingham study estimated that women over 50 years of age, with 2 or more CVD risk factors, had a 50% lifetime risk of developing CVD (Lloyd-Jones, et al., 2006). Physical inactivity and weight gain are two independent risk factors associated with CVD, but have been overlooked when assessing cardiovascular outcomes after adjuvant treatment (Jones, Haykowsky, Swartz, Douglas, & Mackey, 2007). It is reported that 62% of breast cancer survivors are overweight (Irwin, et al., 2005) and 36% are sedentary (Jones, Courneya, Fairey, & Mackey, 2004), while the average age of a breast cancer survivor is 61 (Hayat, Howlader, Reichman, & Edwards, 2007). Based on these estimates, a good percentage of women diagnosed with breast cancer

may already have a significant risk of CVD. Moreover, this risk at diagnosis may be amplified by the combined direct and indirect effects of breast cancer treatment. The direct treatment effects (adjuvant therapy, radiation, hormone therapy) may increase the risk of cardiac dysfunction (ASCO, 2007), but other indirect effects such as weight gain, physical inactivity, and other lifestyle factors may play a role as well. Therefore, it could be speculated that breast cancer survivors may have an elevated risk for CVD, independent of the direct effects of adjuvant treatment, due to their unfavorable risk profile.

1.2 Adjuvant Therapy (Direct Effects)

Cancer treatment may impact the long-term health of survivors (ASCO, 2007), in part due to functional declines in major organ systems including the heart, lungs, muscle, and bones. Cardiovascular disease has been identified as a leading cause of mortality in older female breast cancer survivors. A study by Patnaik et al. followed 63,566 women (66 years of age and older) diagnosed with breast cancer for a median of nine years and revealed that mortality due to CVD was greater than breast cancer (Patnaik, Byers, DiGuseppi, Dabelea, & Denberg, 2011). In addition, CVD remains the major cause of nonmalignant death in long-term survivors of Hodgkin lymphoma who are exposed to cardiotoxic treatment similar to breast cancer therapy (Aleman, et al., 2007).

Chemotherapy agents necessary for treating disease may have lasting effects on the cardiac function of breast cancer survivors. Studies investigating the effects of anthracycline based chemotherapy revealed a 20% to 51% reduction in cardiac function

(Bear, et al., 2006; Bonnetterre, et al., 2004; Martin, et al., 2005; Perez, et al., 2004).

Anthracyclines are a common chemotherapy agent for treating breast cancer, despite their well-known risk for inducing cardiac dysfunction. It is estimated that at least 20% of cancer patients who receive anthracyclines, including the best-known Adriamycin/ Doxorubicin (Dox), experience damage to left ventricular function, which weakens the heart muscle and depletes the organ's pumping strength (Clements, Davis, & Wiseman, 2002). Furthermore, symptoms related to cardiac dysfunction may not manifest for years after treatment (Shan, Lincoff, & Young, 1996). The direct effects of treatment may contribute to a functional decline in the breast cancer survivor's physical capacity, including cardiorespiratory fitness. A reduced physical capacity may lead to increased inactivity and weight gain for the breast cancer survivor.

Adjuvant therapy may also include the long-term use of hormone therapy, including Aromatase Inhibitors (AI). Estrogen plays a central role in the development and progression of breast cancer and AI's are used to prevent the synthesis of estrogen during adjuvant treatment of breast cancer patients and are replacing tamoxifen as the mainstay hormone therapy in post-menopausal breast cancer survivors. AI's have demonstrated to be more effective than tamoxifen due to an improvement in disease free survival and reductions in early distant metastasis, resulting in better overall survival (Janni & Hepp, 2010). In addition, AI's has been recognized to have a "better" risk profile than tamoxifen since they are associated with less life threatening thromboembolic events and endometrial cancer (Howell, et al., 2005). However, estrogen deprivation with AI's may negatively impact lipids, leading to more cardiovascular problems compared to tamoxifen (Smith, 2004).

A meta-analysis including seven randomized controlled trials ($n= 19,818$) revealed a significant increase in the number of cardiovascular events with the use of AI's versus tamoxifen (RR, 1.31; $p = 0.007$) (Cuppone, et al., 2008). AI's can suppress estradiol levels in postmenopausal women by as much as 84%, but they may cause an increase in inflammatory cytokines (Nabholtz, 2008). There is little data available to assess long-term cardiac health while using AI's (Janni & Hepp, 2010) and the cardiac safety of AI's compared to tamoxifen is still unclear. More studies are needed to determine the therapeutic benefit of AI's during adjuvant treatment. A better understanding of the potential for long-term side effects of AI's and their risk-to-benefit ratio is needed because it may impact QoL in breast cancer survivors (Janni & Hepp, 2010).

Cardiorespiratory fitness may suffer as a result of hormone therapy in long-term breast cancer survivors. Suppressing the hormone estrogen may have deleterious physiological effects on the delivery of oxygen to working tissues (Jones, Eves, Haykowsky, Freedland, & Mackey, 2009), possibly modifying the cardiorespiratory fitness of breast cancer survivors. In a study by Jones and colleagues they find that breast cancer survivors treated with AI's had a more unfavorable metabolic profile compared to those treated with tamoxifen. Specifically, breast cancer survivors treated with AI's had a significantly higher BMI (30 ± 6 vs. 26 ± 4 kg/m²), fasting insulin (11.3 ± 5.9 vs. 7.3 ± 4.3 mmol/L), and fasting glucose (5.9 ± 1.2 vs. 5.3 ± 0.5 mmol/L) (Jones, Haykowsky, Pituskin, et al., 2007). A poor metabolic profile may adversely affect cardiac function and diminish the oxidative capacity of working muscle tissue, negatively impacting cardiorespiratory fitness.

Most research in oncology is limited to symptomatic patients during the acute phase of treatment. There is little data demonstrating potential late and long-term cardiac side effects from newer, more targeted therapies that are becoming common practice. Breast cancer patients receiving combination therapy may be most susceptible to compounded cardiac damage but there is limited evidence of any preventive measures that can alter the natural history of cardiac disease in asymptomatic cancer survivors (ASCO, 2007). Thus, combined treatment including chemotherapy and hormonal therapy may increase likelihood of cardiac disease well into survivorship.

1.3 Modifiable Lifestyle Risk Factors (Indirect Effects)

The double impact of treatment (Direct effects) and lifestyle (Indirect effects) can cause a decline in long-term health for breast cancer survivors. Inactivity and increased weight are common lifestyle risk factors experienced by breast cancer patients from the day of diagnosis, throughout treatment, and transitioning into survivorship. It has been previously reported that breast cancer survivors decreased their physical activity by 2 hours per week after diagnosis compared to pre-diagnosis, with a larger decline in physical activity for those receiving adjuvant treatment versus single modality therapy (Irwin, et al., 2003). Investigators have shown that decreased activity may be associated with increased recurrence (Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005; Winzer, Whiteman, Reeves, & Paratz, 2011) and decreased survival. Body Mass Index (BMI) has also been shown to adversely affect survival rates (McTiernan, Irwin, & Vongruenigen, 2010; Protani, Coory, & Martin, 2010). In addition, modifiable risk factors including weight and inactivity have been linked to an increased risk for developing

primary breast cancer. Specifically, obesity was associated with a 63% increased breast cancer risk (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003) and inactivity attributed to a 2-15% elevated risk of breast cancer (Clarke, Purdie, & Glaser, 2006). The double impact of the direct and indirect effects of breast cancer treatment may have a synergistic relationship that leads to an increased chance for breast cancer recurrence and decreased survival.

Current cancer treatments have become effective at treating the malignancy, but may have unintended side effects on long-term health. Late and long-term effects of cancer treatment include pain, cancer related fatigue, and diminished cardiorespiratory fitness (Courneya & Friedenreich, 2001). Additionally, breast cancer treatment is associated with physiological effects on body systems including pulmonary, cardiac, and musculoskeletal function, thus contributing to decreased activity (K. Schmitz, 2011). Declining physical activity related to the effects of cancer treatment may contribute to the diminished cardiorespiratory fitness and increased weight observed in these individuals.

Physical risk factors including decreased cardiorespiratory fitness and increased fat mass may contribute to dysregulated metabolic factors that negatively impact long-term health of breast cancer survivors. Excess weight and physical inactivity can raise circulating levels of insulin (Eheman, et al., 2012). Chronic high insulin levels may play an independent role in tumorigenesis (Donohoe, Doyle, & Reynolds, 2011; Gallagher & LeRoith, 2011) and may increase risk of breast cancer and all-cause mortality (Goodwin, et al., 2002). In addition, cardiovascular mortality is increased among insulin resistant patients (Huisamen, et al., 2012).

Breast Cancer and Weight Gain

Weight gain in breast cancer survivors has been shown to significantly increase cardiovascular disease mortality (Nichols, et al., 2009). For example, each 5-kg gain in weight after breast cancer diagnosis was associated with a 12%, 13%, and 19% increase in all-cause, breast cancer, and CVD mortality, respectively (Nichols, et al., 2009). In addition, breast cancer survivors with a BMI greater than 25 kg/m² have up to a 60% increased risk for death compared to survivors with normal body weight (Saxton, et al., 2006). Breast cancer survivors undergoing adjuvant chemotherapy experience an increase in fat mass (a component of BMI), with no change or decrease in lean mass, known as sarcopenic obesity (Demark-Wahnefried, et al., 2001). This change in body composition may create a physical environment rich in metabolic factors that adversely affect the health of breast cancer survivors.

Overweight/obesity may influence the mechanisms that can play a role in breast cancer and CVD risk. Overweight/obesity is associated with higher concentrations of endogenous estradiol, insulin, and inflammatory markers (Renehan, Roberts, & Dive, 2008). In turn, risk factors including elevated BMI (Renehan, Tyson, Egger, Heller, & Zwahlen, 2008), central adiposity (Harvey, et al., 2005), elevated glucose (Muti, et al., 2002), and insulin (Goodwin, 2008; Patterson, Cadmus, Emond, & Pierce, 2010), have an association with breast cancer and CVD risk. Obesity is dependent on the percent body fat (adipose tissue), and adipose tissue is the main source of estrogen biosynthesis in postmenopausal women (Baer, et al., 2005). In addition, estradiol is a potent physiological form of estrogen, and is synthesized in adipose tissue. The risk for developing breast cancer can increase five-fold when estradiol levels increase from 5

pg/ml to 11 pg/ml. Therefore, lifestyle related risk factors may contribute to an increase in metabolic risk factors associated with breast cancer and CVD risk.

Breast Cancer and Low Cardiorespiratory Fitness

Inactivity may lead to a low cardiorespiratory fitness level (measured as VO_{2max}) contributing to all-cause (Blair, et al., 1989) and cardiovascular (Blair, et al., 1996) mortality. Specific to CVD, decreased physical activity levels have a strong association with CVD in breast cancer patients, indicating that interventions to improve cardiorespiratory fitness may be important (Jones, Haykowsky, Pituskin, et al., 2007). In addition, women with a low fitness level can be at greater risk for breast cancer mortality. Alarming, women without a history of cancer who underwent a maximal exercise test and performed at 8 METS (28 ml/kg/min VO_2) or below had nearly a three-fold increased chance of breast cancer mortality compared to those who reached a level above 28 ml/kg/min VO_2 (Peel, et al., 2009). Using a standardized measure of cardiorespiratory fitness will be helpful to quantify the effectiveness of an exercise program for breast cancer survivors (McNeely, et al., 2006). Cardiorespiratory fitness can be objectively measured with VO_{2max} , and VO_{2max} has been associated with CVD occurrence and breast cancer mortality (Speck, Courneya, Masse, Duval, & Schmitz, 2010). Efforts should be made to improve cardiorespiratory fitness in breast cancer survivors in order to increase the likelihood for healthy outcomes.

There is a paucity of data that describes cardiorespiratory fitness in long-term breast cancer survivors. More studies are needed to identify any association between cardiorespiratory fitness with breast cancer and CVD risk in breast cancer survivors who

are 5 years, 10 years, and longer post-treatment. Also, it would be beneficial to measure cardiorespiratory fitness at time of diagnosis to explore any decline over the continuum of care in breast cancer survivors. Our findings within this dissertation highlight the need for healthy lifestyle change in breast cancer survivors due to low cardiorespiratory fitness.

1.4 Exercise and Breast Cancer Survivors

Regular physical exercise may reduce the risk of death from recurrence of breast cancer in survivors (Holmes, et al., 2005). It is important to note that low levels of physical activity may be the most modifiable of all the plausible risk factors for breast cancer (Neilson, Friedenreich, Brockton, & Millikan, 2009). In addition, exercise has been shown to have a positive effect on breast cancer risk factors including decreased estrogen (Lynch, Neilson, & Friedenreich, 2011; Neilson, et al., 2009; Winzer, et al., 2011) and decreased insulin (Friedenreich, et al., 2011; Winzer, et al., 2011).

Physical activity is being investigated to determine its effectiveness for improving long-term health in breast cancer survivors. The indirect effects of cancer treatment can have a negative impact on breast cancer survivors' health and quality of life. A recent review focusing on physical activity, diet, and adiposity pointed out that in breast cancer survivors, increased adiposity appeared to be associated with a 30% increase in mortality and an increase in physical activity with a 30% decrease in mortality (Patterson, et al., 2010). Even though modifiable lifestyle factors are achievable, a majority of breast cancer survivors are overweight or obese (Pinto, et al., 2002). Only 39% indicated they consumed a low-fat diet and exercised at recommended levels

(Pinto, et al., 2002). Breast cancer survivors who modify their lifestyle with diet and exercise may have a better long-term QoL compared to those who continue to gain weight and remain inactive. A study performed by Pierce and colleagues showed that breast cancer survivors who engaged in both healthy diet and exercise behaviors had a 50% reduced risk of all-cause mortality (Pierce, et al., 2007).

Research indicates exercise provides health benefits positively affecting breast cancer and CVD risk factors for breast cancer survivors. Lifestyle interventions including diet and exercise improved weight, fat mass, lean mass, and lipids for breast cancer survivors (Irwin, et al., 2009; Mefferd, Nichols, Pakiz, & Rock, 2007; K. H. Schmitz, Ahmed, Hannan, & Yee, 2005; Thomson, et al., 2010). In a study recently completed by our team of investigators (Klemp JR, 2009), we found that post-menopausal overweight breast cancer survivors who participated in a 6-month structured diet, exercise, and behavioral intervention lost an average of 11% of their initial body weight, >5% fat mass, and had a four-fold increase in their minutes of cardiovascular exercise (Klemp JR, 2009). Systematic reviews and meta-analysis revealed that a majority of the studies including exercise interventions had a positive and significant impact on aerobic fitness during and post cancer treatment (Galvao & Newton, 2005; McNeely, et al., 2006; Speck, et al., 2010).

To our knowledge, there have been no studies investigating the improvement in VO_{2max} and additional breast cancer or CVD risk factors in breast cancer survivors when comparing between weight loss alone, exercise alone, or weight loss plus exercise. However in a recent 12-week randomized intervention, obese participants were randomized to exercise only, calorie restriction only, or exercise and calorie restriction.

The results indicated a significant increase in VO_{2max} from the exercise alone or the combined exercise and calorie restriction intervention (14% and 18%, respectively), but found no change in VO_{2max} in the calorie restriction alone group (Christiansen, Paulsen, Bruun, Pedersen, & Richelsen, 2010). In a similar 6-month intervention in overweight (non-cancer) participants, caloric restriction only versus caloric restriction plus aerobic exercise versus weight maintenance diet, VO_{2max} significantly improved (increased) in the caloric restriction plus aerobic exercise arm only, $22 \pm 5\%$ vs $7 \pm 5\%$ (caloric restriction alone), vs $-5 \pm 3\%$ (weight maintenance diet) (Larson-Meyer, Redman, Heilbronn, Martin, & Ravussin, 2010). Based on these previous studies, interventions targeting cardiorespiratory fitness may not significantly improve VO_{2max} without the exercise component.

The evidence is growing relating to the positive effects of exercise in breast cancer survivors as depicted in the previously mentioned studies. In addition, a recent meta-analysis revealed sixty-six high quality studies investigating the positive impact physical activity has on several outcomes including body weight and cardiorespiratory fitness in a heterogeneous group of cancer patients and survivors (Speck, et al., 2010). A more recent review focusing only on cancer survivorship, rather than during and post treatment, revealed that diet only interventions improved diet quality, nutrition-related biomarkers, and body weight while exercise only interventions improved fitness, strength, physical function, and psycho-social variables (Pekmezi & Demark-Wahnefried, 2011). The American Cancer Society advocates combining diet and exercise interventions, but few studies involving combined interventions are available.

Specifically, there have been five randomized controlled trials performed in the last three years incorporating combined diet and exercise interventions (Table 1.1).

Although, the two recent reviews supported exercise interventions for cancer patients and during survivorship, the authors concluded important questions remain to be unanswered. First, more work is needed to help us understand the dose of exercise to generate the greatest improvement in targeted outcomes. Expanding our knowledge on the dose response of exercise training can assist us in developing specific exercise guidelines for cancer survivors. Next, the reviewers noted that they did not account for the possible differences between supervised versus home-based exercise interventions (Speck, et al., 2010).

Two studies in the review conducted by Pekmezi et al. involved breast cancer survivors, but none included cardiovascular exercise dosing to determine improvements in cardiorespiratory fitness in the design. In addition, none of the studies included VO_{2max} for measuring improvement in cardiorespiratory fitness. Jones and colleagues are studying the effects of cardiovascular exercise dose intensity on VO_{2max} in breast cancer survivors during a supervised intervention (Jones, et al., 2010). In contrast to Jones' study, this dissertation will use a home-based intervention to investigate the effects cardiovascular exercise dose intensity has on VO_{2max} . Therefore, the environment where the exercise training may have the best chance of achieving sustainability should be considered.

1.5 Home-Based Exercise Program

Four of the five studies reviewed by Pekmezi et al. indicate a trend in home-based and semi-supervised interventions. Lifestyle change including diet and exercise may be more sustainable when the interventions are home-based and semi-supervised (Pekmezi & Demark-Wahnefried, 2011). From a practical point of view, it's difficult for many adults to balance work, kids, domestic life, and a scheduled supervised exercise program into their weekly regimen. Many breast cancer survivors may find it difficult to sustain any fitness gains made from a supervised exercise program since they may not be able to maintain routine visits to monitored sessions. Therefore, we should caution recommending exercise dose prescription based on small samples of people from supervised studies, when comparing such studies to the general home-based activity preference of breast cancer survivors (Blair, LaMonte, & Nichaman, 2004).

It seems appropriate to design exercise interventions that support the needs of the target population if we eventually want to reach a large number of breast cancer survivors. When designing interventions for breast cancer survivors we should consider environmental factors that may influence exercise preferences (Rogers, Courneya, Verhulst, Markwell, & McAuley, 2008). A home-based intervention to promote exercise has been preferred over visiting a fitness facility or cancer center by a majority of the breast cancer survivors (Jones & Courneya, 2002; Rogers, Courneya, Shah, Dunnington, & Hopkins-Price, 2007; Rogers, Markwell, Verhulst, McAuley, & Courneya, 2009). Therefore, it's possible interventions focusing on the promotion of exercise in the home environment will help increase adherence to behavior change in a larger number of breast cancer survivors.

Ultimately, we would like to see a favorable exercise adherence rate in home-based studies to assure efficacy of the prescribed intervention. Prior studies have investigated adherence to home-based exercise interventions with mixed results. A previous study by Duncan et al. showed that adherence to prescribed exercise ranged from an undesirable 57.8% - 68.8% during a home based intervention for sedentary adults (Duncan, et al., 2005). However, another study by King et al. showed that a home-based exercise program produced a significantly higher ($P < 0.001$) adherence rate versus a supervised community based program in healthy sedentary adults (King, Haskell, Taylor, Kraemer, & DeBusk, 1991). In addition, home-based interventions have produced similar improvements in VO_{2peak} and exercise participation in obese women and sedentary adults compared to a supervised group exercise program (King, et al., 1991; Perri, Martin, Leermakers, Sears, & Notelovitz, 1997).

This study will provide the next steps in developing future home-based exercise prescriptions for breast cancer survivors to improve targeted outcomes including CVD and breast cancer risk factors. Targeting breast cancer and CVD risk factors seems plausible since recurrence is the leading cause of mortality, and CVD incidence increases in survivors (ASCO, 2007). Furthermore, it is still unclear what dose of exercise would be the safest and most effective dose to achieve the most meaningful improvement in targeted outcomes (Galvao & Newton, 2005). There is a lack of evidence investigating the most effective exercise dose-response to improve quality of health in breast cancer survivors (McNeely, et al., 2006) and we need to tailor exercise interventions to focus on type (K. Schmitz, 2011) and dose (Lynch, et al., 2011) of exercise that may relate to reducing breast cancer and CVD risk. This study aims to

address these limitations by exploring feasibility of two different cardiovascular exercise doses during a home-based exercise program (Aim 1), and determining the impact cardiovascular exercise dosing has on improving VO_{2max} and weight loss (Aim 2). We'll use an exercise methodology to investigate the role of cardiovascular dose-intensity exercise for breast cancer survivors.

Assessing cardiorespiratory fitness by measuring VO_2 provides an accurate tool for identifying the success of an exercise program. An objective measure of fitness is essential to accurately assess improvement after an exercise intervention, as well as, respond to the need for a standardized measure of fitness in breast cancer survivors (McNeely, et al., 2006). To our knowledge, no studies in breast cancer survivors include the gold standard cardiorespiratory fitness measure (VO_{2max}) to assess baseline and changes after an Energy Balance Program. We plan to measure VO_{2max} during a cardiorespiratory test, while assessing the feasibility of two separate cardiovascular exercise dose intensities during an Energy Balance Program. Cardiorespiratory testing can provide an objective evaluation of fitness, reducing the variability found in self-reported activity measures by 70-80% (Blair & Church, 2004). Therefore, we'll be able to quantify cardiorespiratory fitness change after using two separate cardiovascular exercise dose intensities during an Energy Balance Program for breast cancer survivors.

1.6 Cardiovascular Exercise Dose Response

Two exercise intensity doses include Moderate Continuous Training (MCT) and Interval Training (IT). Clinical practice may benefit from a better understanding of a

specific training dose to produce the best health outcomes in breast cancer patients. An earlier review indicated that more prospective studies are needed to investigate exercise dosing in cancer populations as a whole (Galvao & Newton, 2005). MCT focuses on an aerobic exercise intensity at or near 50-70% of maximal achieved Heart Rate (HR). MCT is aerobic in nature and has effectively reduced all-cause and cardiac mortality rates (Jolliffe, et al., 2000). Evidence suggests the training characteristic of MCT improves aerobic capacity mostly due to oxygen extraction at the muscle (Daussin, et al., 2008).

In contrast, IT produces a training dose that includes aerobic and anaerobic metabolic demands, involving perturbations of exercise intensity within an approximate 60-95% of maximal achieved HR. IT benefits both anaerobic and aerobic systems allowing a better response to peak aerobic fitness than MCT due to cardiac and skeletal muscle metabolic demands (McArdle, 2007). Cardiac function may be improved with short bouts of anaerobic activity while meeting the essential need of more blood flow to working skeletal muscle. Cardiac performance can be enhanced with anaerobic exercise due to improvement in left ventricular filling and contractility (stroke volume) (Wigmore, 2011), with filling providing a good portion of enhanced cardiac function leading to an elevated cardiac output (CO) (Ferguson, Gledhill, Jamnik, Wiebe, & Payne, 2001; Gledhill, Cox, & Jamnik, 1994). Improvement of diastolic function as identified by augmented left ventricular filling is important since diastolic dysfunction has been theorized to be a major effect of chemotherapy induced cardiotoxicity (Shan, et al., 1996). This dissertation explores if IT may be a cardiovascular exercise dose-response that improves VO_{2max} to a greater extent than MCT.

IT: From Cardiac Function to Cardiorespiratory Fitness

The double impact of breast cancer treatment may lead to diminished ventricular function, resulting in a diminished QoL for breast cancer survivors. The combined effects of toxicity and inactivity may weaken the heart muscle of breast cancer survivors. This cardiac dysfunction can be caused by dilated ventricles and a decrease in ventricular wall thickness inducing a diminished stroke volume (Wigmore, 2011), ultimately resulting in a reduction of CO and increased workload on the heart during activity. Breast cancer survivors had less available blood delivered to their working muscles compared to non-cancer peers due to a reduced CO (10.4 ± 1.5 vs. 11.7 ± 2.4 L/min, $P = 0.02$) during maximal cardiorespiratory testing on a cycle ergometer (Jones, Haykowsky, Pituskin, et al., 2007). If ventricular function is compromised in cancer survivors, usually due to the effects of dilated cardiomyopathy (ASCO, 2007), dysfunction of ventricular contractility and relaxation will limit the working muscles of the required blood flow to meet the energy demands during exertion. This deficit in blood flow to working tissues may lead to early onset fatigue, shortness of breath, and ultimately a diminished exercise capacity.

Interval training may improve stroke volume, and ultimately cardiorespiratory fitness, more than MCT in breast cancer survivors. Ability to increase CO depends on heart rate and stroke volume, with stroke volume contingent on ventricular filling and contractility. As exercise intensity progresses into an anaerobic state, stroke volume increases secondary to increased contractility of the left ventricle. Adaptations including contractility of the left ventricle will increase amount of oxygenated blood available to working muscles. Whole body oxygen consumption (VO_{2max}) will increase in proportion

to exercise intensity and is a result of cardiac output (CO) and skeletal muscle oxygen uptake (Wigmore, 2011). Physiological adaptations to IT can include a more efficient stroke volume due to the increasing metabolic demands of working muscle as a result of a higher exercise intensity. The human body may adapt to the physiological stress induced by different exercise intensities. Ultimately, anaerobic exercise during IT induces physiological changes including cardiac function, leading to improved VO_{2max} .

IT and Cardiorespiratory Fitness

There is a limited amount of data on IT in female populations, but IT has shown to significantly improve VO_{2max} in children (Baquet, et al., 2010), sedentary adults (Daussin, et al., 2008), pulmonary patients (Arnardottir, Boman, Larsson, Hedenstrom, & Emtner, 2007), CAD patients (Moholdt, et al., 2009; Rognmo, Hetland, Helgerud, Hoff, & Slordahl, 2004; Warburton, et al., 2005; Wisloff, et al., 2007), heart failure patients (Dimopoulos, et al., 2006; Nechwatal, Duck, & Gruber, 2002), and adults with metabolic syndrome (Tjonna, et al., 2008). Table 1.2 shows ten separate randomized trials in the past ten years that used IT in different populations. To the best of our knowledge, no studies have been completed on breast cancer patients that use IT. However, one such study is currently investigating the effects of IT on breast cancer and CVD risk factors in breast cancer survivors during a highly supervised intervention (Jones, et al., 2010).

Interval training may help enhance tolerance to exercise due to greater improvement of cardiac function and oxygen uptake (VO_{2max}) compared to MCT. In a study with sedentary adults, IT was involved with greater changes within groups in CO and VO_{2max} from baseline and significantly greater ($P < 0.05$) improvements between

groups in time to exhaustion, ultimately leading to greater changes within groups in $\text{VO}_{2\text{max}}$ (Daussin, et al., 2007; Daussin, et al., 2008). Eleven sedentary subjects (7 men and 4 women) were assigned to either a MCT or an IT program. The training consisted of 3 sessions per week for 8 weeks. After the initial training program, all subjects went through a detraining period of 12 weeks, then reassigned in a randomized cross-over design to the opposite training regimen from their initial program. The duration of the MCT and IT program was equal, building up to 35 minutes per session over the last 2 weeks. The IT program included blocks of 5 minutes with 4 minutes at power output (watts) achieved at the ventilatory threshold (VT) and 1 minute at 90% of peak power output. VT and peak power output were determined from a maximal cardiorespiratory exercise with gas analysis performed on a bike ergometer. MCT was performed at the power output consistent with power achieved at VT, based on the following formula: $[4 \times P_{\text{VT1}} + 90\% \text{ of } P_{\text{max}}/5]$ (Daussin, et al., 2008). The prescribed intensities of both programs allowed for similar energy expenditures. IT appeared to improve functional exercise capacity due in part to significant changes in CO from baseline.

Much of the past work comparing IT to MCT includes patients with a cardiac history. Warburton et al. showed that IT revealed higher functional performance versus MCT in patients with a history of CAD, revealing a significant greater improvement ($p < 0.05$) in time to exhaustion. In a previous study, 14 men with a history of CAD (> 6 months) who underwent bypass surgery or angioplasty were stratified by age, BMI, and $\text{VO}_{2\text{max}}$ (Warburton, et al., 2005). Subjects were randomized to a traditional cardiac rehab model consisting of MCT or an IT program. Both programs consisted of the same warm-up, standardized resistance training, and cool-down. The aerobic training in the

MCT consisted of 30 minutes of aerobic exercise at 65% of HR/VO₂ reserve, while the IT program included 2 minute bouts of increased intensity at 90% HR/VO₂ reserve followed by 2 minute recovery bouts at 40% HR/VO₂ reserve. Both groups trained 30 minutes per day, 2 days per week, for 16 weeks. Aerobic training involved 3 separate 10 minute bouts on 3 different types of cardiovascular exercise equipment, for a total of 30 minutes. It is important to note that a systematic review of patients with a history of CAD (range 4 weeks to 12 months post-MI) who performed interval training reported that no adverse cardiac events took place in 213 participants (180 men and 33 women) in 7 separate studies (Cornish, Broadbent, & Cheema, 2010).

Another randomized study with cardiac patients assessed IT versus MCT, for increasing VO_{2max} (Rognmo, et al., 2004). Rognmo et al. studied 17 CAD patients (14 men and 3 women) who had a past (> 12 months) coronary artery bypass graft or MI. Training consisted of treadmill walking 3 x per week, for 10 weeks. Total training load was equal, but the IT group exercised in 4 minute bouts of higher intensity, equal to 85-95% peak HR (80-90% VO_{2 max}) achieved on a baseline maximal cardiorespiratory exercise test on a treadmill. The IT group exercised at 50-60% VO_{2max} during the remainder of each exercise session. The MCT group remained at 50-60% of VO_{2max} for their entire exercise session. Total training load was balanced by the MCT group exercising longer than the IT cohort. The main outcome measure, VO_{2max}, increased significantly more ($p = 0.01$) in the IT versus the MCT group after the 10 week intervention. The outcomes from sedentary and cardiac populations provide evidence that IT can be more effective for improving functional exercise capacity secondary to greater increases in CO and VO_{2max}.

Interval training has been effective at improving VO_{2peak} significantly greater compared to MCT in supervised interventions for populations other than breast cancer survivors (Daussin, et al., 2008; Rognmo, et al., 2004; Tjonna, et al., 2008; Warburton, et al., 2005; Wisloff, et al., 2007). Yet, currently there has not been a study investigating the efficacy of IT in the home-based environment. The previous studies on IT provide a foundation for hypothesizing that IT may enhance cardiorespiratory fitness and improve health outcomes for breast cancer survivors. We aim to identify the feasibility of using IT and MCT during an Energy Balance Program (Aim 1) and determine the impact of cardiovascular exercise dosing on improving VO_{2max} and weight loss while using IT and MCT dosing methodology (Aim 2).

1.7 Significance of Research

Diet and exercise interventions have shown to improve CVD and breast cancer risk factors in breast cancer survivors. To our knowledge, no prior studies have examined the response to different cardiovascular exercise doses including IT during a home-base intervention in this high-risk population. This gap in the literature exists despite growing evidence supporting IT as an effective means to improve cardiorespiratory fitness in chronic diseases, including CVD. However, a scarcity of data is available in the field of cancer survivorship.

Results from this study can contribute to the current literature on the feasibility of cardiovascular exercise dose prescription for breast cancer survivors in a home-based study. This dissertation project will provide novel information on two different cardiovascular exercise dose intensities prescribed during a home-based intervention

for breast cancer survivors, while determining the impact on improving $VO_{2\max}$ and weight loss. The work presented in the following chapters can serve as a foundation for further studies exploring the impact of IT on cardiorespiratory fitness in breast cancer survivors.

1.8 Specific Aims and Statement of Hypotheses

Breast cancer treatment can have adverse effects on lifestyle related risk factors including inactivity and body composition. Inactivity can serve as a precursor for low cardiorespiratory fitness and weight gain. Combined diet, exercise and lifestyle behavior modification (Energy Balance Program) may influence health related outcomes during breast cancer survivorship, what is not clear is the most effective exercise dose to elicit the greatest improvement in targeted risk factors during an Energy Balance Program.

This dissertation project was conducted to contribute to a need that was established from preliminary work investigating cardiorespiratory fitness in breast cancer survivors. Initially, we determined that breast cancer survivors had a low cardiorespiratory fitness level when compared to age-matched healthy normal values; and submaximal testing on a treadmill and elliptical trainer had a strong correlation to the “gold standard” test for measuring cardiorespiratory fitness on a treadmill (Chapter 2). The overarching goal of this project was to develop a clinically effective and feasible exercise strategy for improving in $VO_{2\max}$ and weight loss during an Energy Balance Program for breast cancer survivors. The overall objective of this dissertation was to determine whether cardiovascular exercise dosing during an Energy Balance Program

is feasible and will have different effects on $VO_{2\max}$ and weight loss. Our central hypothesis is that breast cancer survivors will be able to adhere to cardiovascular exercise dosing including MCT and IT; and IT will elicit greater improvements on $VO_{2\max}$ and weight loss compared to MCT during an Energy Balance Program. The rationale for the proposed research is that, once the feasibility of cardiovascular exercise dosing is known, effective exercise prescription can be made for breast cancer survivors, resulting in an innovative approach to address cardiorespiratory fitness and weight loss. Two central aims guide this dissertation research:

Specific Aim # 1: Determine the feasibility of two separate exercise doses, IT and MCT, in breast cancer survivors while they participate in a 17-week Energy Balance Program (Chapter 3).

If breast cancer survivors can use exercise dosing prescription during an Energy Balance Program, then greater improvements in risk factors for CVD and breast cancer may occur. It was hypothesized that breast cancer survivors will be able to participate in exercise dosing using MCT and IT during an Energy Balance Program, as evidenced by adherence to prescribed exercise time and intensity. The results demonstrated that participants were able to adhere to their prescribed exercise dose time and intensity during an Energy Balance Program. These results suggest that exercise dosing can be used in an Energy Balance Program.

Specific Aim # 2: Identify the impact of two separate cardiovascular exercise doses on improving VO_{2max} and weight loss, comparing baseline to post-intervention values

(Chapter 3).

Because no studies have previously examined the usefulness of cardiovascular exercise dose intensity during a home-based intervention, we aimed to compare mean within- and between-group changes in VO_{2max} and weight after breast cancer survivors participated in an Energy Balance Program. We hypothesized that, if differences were identified, IT would elicit a more favorable response for improved VO_{2max} versus MCT. Results showed that significant improvements occurred in VO_{2max} and weight loss after a 17 week Energy Balance program using cardiovascular exercise dose prescription. Furthermore, IT elicited a significantly greater improvement in VO_{2max} compared to MCT. Results suggest that IT can elicit greater improvements in VO_{2max} than MCT for breast cancer survivors.

In summary, the research presented in this dissertation contributes to the field of breast cancer survivorship in two separate manuscripts. These manuscripts provide unanswered questions relating to important health outcomes for breast cancer survivors: 1) demonstrate cardiorespiratory fitness level in breast cancer survivors (Chapter 2, prepared for submission to *Breast Cancer Research and Treatment*, 2) submaximal exercise testing may be an alternative to maximal testing for objectively measuring cardiorespiratory fitness in breast cancer survivors (Chapter 2), 3) feasibility of cardiovascular exercise intensity dosing during an Energy Balance Program (Chapter 3, to be submitted to *Cancer Prevention Research*), and 4) impact of cardiovascular exercise dosing on improving VO_{2max} and weight loss (Chapter 3).

Tables and Figures

Table 1.1 Diet and Physical Activity Randomized Controlled Trials.

Five randomized controlled trials of combined diet and physical activity over a three year span (2007-2010). *Modified from:* (Peckmezzi & Demark-Wahnefried, 2011).

Author	Sample	Intervention	Frequency, intensity, Duration	Results
Bloom et al. 2008	404 female BrCa survivors and a wait list control group.	Supervised 30 minute resistance exercise and yoga sessions, group walks, healthy diet handouts.	Three six-hour workshops over three months.	Intervention group was more likely to report increased physical activity vs. the control group ($p=0.036$), but not diet changes.
Cambell et al. 2009	266 Colorectal cancer survivors and 469 controls. 2x2 design testing tailored print, telephone interviewing, or both vs. control of standardized print material.	Promotion of physical activity and fruit and vegetable consumption	Tailored print material consisted of four newsletters delivered over nine months and telephone interviewing consisted of 4-20 minute calls over nine months.	Combined intervention produced the greatest changes in fruit and vegetable consumption, but this effect was seen in controls and not in colorectal cancer survivors. No changes in weight or physical activity were observed.

Author	Sample	Intervention	Frequency, intensity, Duration	Results
Denmark-Wahnefried et al. 2008	90 newly diagnosed BrCa survivors scheduled for chemo. Three-armed trial (attention control) vs. exercise + low fat, plant-based diet.	Diet counseling aimed at decreasing fat and at least 5 fruit and vegetables per day. Exercise counseling promoting greater than 30 minutes of exercise per day at least 3 days per week.	All participants received written mailed materials and telephone counseling including 14 sessions over a six month period.	Fat and fruit and vegetable scores differed significantly in the diet + exercise arm; though no differences in change scores were observed for physical activity.
Morey et al. 2009	641 older, overweight colorectal, breast, and prostate survivors. Diet-exercise intervention vs. wait list control.	Telephone counseling and mailed print material-based diet and exercise intervention.	12 month program with personally tailored workbook quarterly newsletters, 15 telephone sessions. Goals = 15 minutes strength training every other day, 30 minutes/day endurance exercise, 7-9 fruits and vegetable servings per day.	Physical activity, weight loss, dietary behaviors, and overall quality of life improved significantly in the intervention group compared with the control.

Author	Sample	Intervention	Frequency, intensity, Duration	Results
von Gruenigen et al. 2008	45 overweight/obese endometrial cancer survivors. Diet-exercise intervention vs. wait list control.	Lifestyle intervention involving group and individual physical activity and nutritional counseling with behavior modification.	Six month program with groups meeting weekly for six weeks, bi-weekly for one month, and monthly for three months, with calls or newsletters on weeks groups did not meet. Goal = aerobic activity five days/week for 45 minutes or more and 5% weight loss.	Intervention group showed significantly greater improvements in weight and physical activity than the control group (p-values <0.05).

Table 1.2 Interval Training Trials.

Ten separate trials using interval training from the past decade.

Authors	Sample	Design	Intervention Duration and Environment	Results
Daussin et al. (2008)	Eleven sedentary adult subjects.	Randomly assigned to one of two 8-wk training programs in a cross-over design, separated by 12 weeks of detraining.	Three sessions per week for 8 weeks. (Supervised)	Maximal oxygen uptake (Vo2max) increased after both trainings (9% with CT vs. 15% with IT).
Arnardottir et al. (2006)	Sixty adult COPD patients.	Randomly assigned to an interval (IT) or continuous (CT) training rehabilitation program.	Two sessions per week for 16 weeks. (Supervised out-patient)	VO2 peak significantly improved in IT group ($p<0.05$) and MCT group ($p<0.001$) after the exercise program. There were no significant differences between groups.
Dimopoulos et al. (2006)	Twenty-four stable CHF patients.	Randomly assigned to an interval (IT) or continuous (CT) training rehabilitation program.	Three sessions per week for 12 weeks. (Supervised rehabilitation)	Both groups significantly improved VO2 peak: (CT: 6% increase, $P=0.01$); (IT: 8% increase, $P=0.01$).

Authors	Sample	Design	Intervention Duration and Environment	Results
Moholdt et al. (2009)	Fifty-nine CABG patients.	Randomly assigned to aerobic interval (AIT) or moderate continuous training (MCT).	Five sessions per week for 4 weeks. (Supervised rehabilitation) Followed by 6 months of home-based exercise.	VO2 peak increased between baseline and 4 weeks in AIT ($P < .001$) and MCT ($P < .001$); group difference was not significant after 4 weeks of supervised rehab. VO2 peak in AIT group significantly improved between 4 weeks and 6 months ($P < .001$), with no significant change in MCT.
Nechwatal et al. (2002)	Fifty chronic heart failure patients	Randomized 3 group design. Steady state vs. interval training vs. control group.	Three week trial. (Supervised)	VO2 peak at the anaerobic threshold and at maximal exercise increased in the continuous exercise group: 13.7% ($p < 0.05$) and 9.3% ($p < 0.05$). In the interval training group the increase was 14% ($p < 0.05$) and 8.1% ($p < 0.05$).
Rognmo et al. (2004)	Twenty-one stable CAD patients.	Randomized to a high intensity or moderate intensity exercise training group.	Three times per week for 10 weeks. (Supervised)	VO2 peak increased by 17.9% ($P=0.012$) in the high intensity group and 7.9% ($P=0.038$) in the moderate intensity group. The training-induced adaptation was significantly higher in the high intensity group ($P=0.011$).
Tjonna et al. (2008)	Thirty-two metabolic syndrome patients.	Randomized 3 group design. Continuous moderate exercise(CME) vs. aerobic interval training (AIT) vs. control group.	Three times per week for 16 weeks. (Supervised)	VO2 peak increased more after AIT than CME (35% versus 16%; $P<0.01$).

Authors	Sample	Design	Intervention Duration and Environment	Results
Warburton et al. (2005)	Fourteen men who had bypass surgery or angioplasty ≥ 6 months prior to exercise training.	Randomly assigned to traditional rehabilitation or interval training.	Two days per week for 16 weeks. (Supervised)	Both groups significantly improved VO ₂ peak: ($P < 0.05$), but no between-group difference in degree of change. The interval training group showed a significantly greater improvement in VO ₂ at anaerobic threshold compared to the traditional rehabilitation group ($P < 0.05$).
Wisloff et al. (2007)	Twenty-seven patients with stable post-MI heart failure.	Randomized to moderate continuous training (MCT) or aerobic interval training (AIT) group.	Three sessions per week for 12 weeks. (Supervised x 2 per week and 1 x per week at home)	VO ₂ peak increased more with AIT than MCT (46% versus 14%, $P < 0.001$).
Baquet et al. (2010)	Sixty-three children.	Randomized 3 group design. Continuous (CTG) vs. intermittent (ITG) running training vs. control group (CG).	Participants in the CTG and ITG groups performed 3 training sessions per week for 7 weeks. (Supervised)	VO ₂ peak was significantly improved in CTG (+7%, $p < 0.001$) and ITG (+4.8%, $p < 0.001$), whereas no difference occurred for the CG (-1.5%).

Figure 1.1 Modifiable Risk Factors that can Increase the Chance for Breast Cancer and the Incidence of CVD

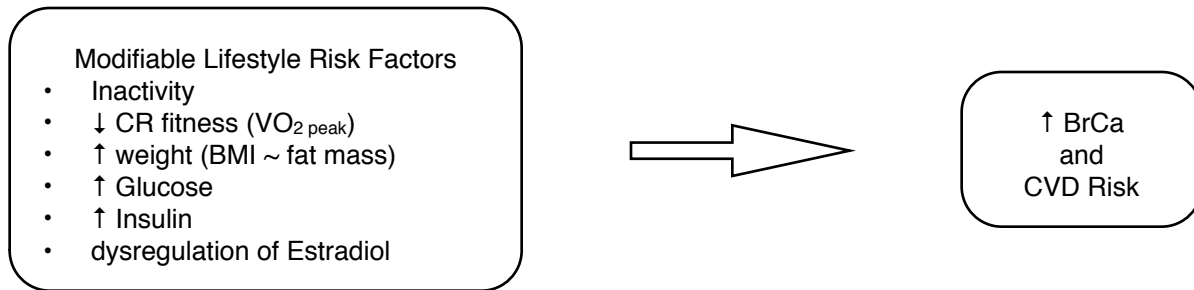
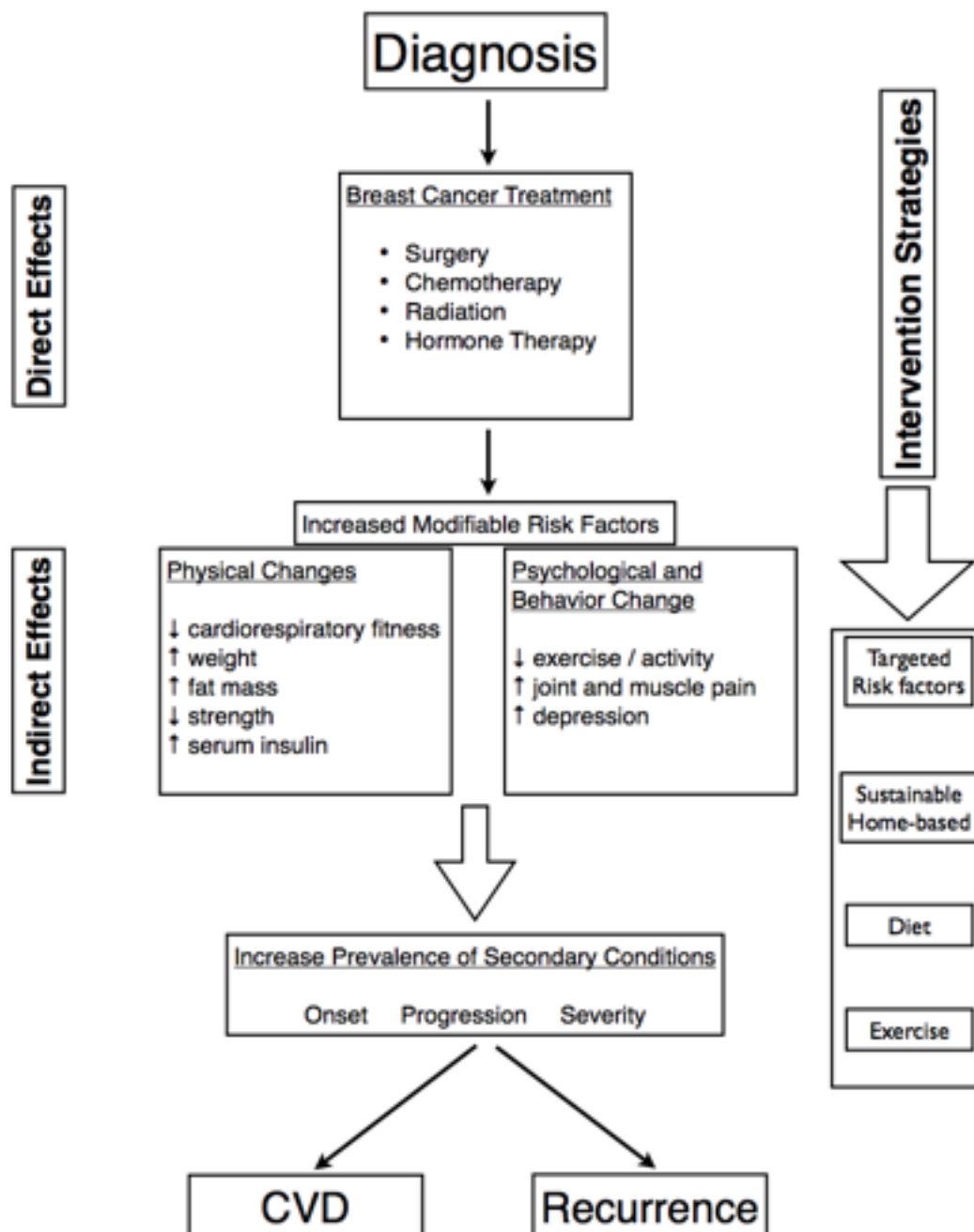


Figure 1.2 Breast Cancer Survivors Disease Prevention Model

Conceptual model of the two leading causes of mortality in breast cancer survivors and an intervention strategy to help prevent disease onset. The Indirect and direct effects of the breast cancer treatment experience can have a negative impact on survivors' health outcomes. Home-based combined diet and exercise interventions are proposed to improve targeted risk factors.



Chapter 2

Measurement of Cardiorespiratory Fitness in Breast Cancer Survivors

2.1 Introduction

More than 290,000 women were estimated to be diagnosed with breast cancer in 2011, and the number of survivors has risen beyond 2.5 million (ACS, 2011). There is an excess risk of cardiovascular deaths in women with breast cancer which is the second most common cause of death in breast cancer survivors (Eloranta, et al., 2012). The excess in risk of cardiovascular death is likely due to physical inactivity and weight gain as well as side effects of treatment (Ewer, Swain, Cardinale, Fadol, & Suter, 2011; Jones, Haykowsky, Swartz, et al., 2007). Women with low cardiorespiratory fitness measured during a graded maximal exercise test and assessment of maximal oxygen consumption, or VO_{2max} , have both an increased risk of cardiovascular and breast cancer deaths (Blair, et al., 1996; Blair, et al., 1989; Peel, et al., 2009). Women with low cardiorespiratory fitness (below VO_{2max} of 8 METS or $28 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1} \text{ } VO_2$) had a nearly 3 fold increase in breast cancer deaths compared to those who reached a level above 8 METS (Peel, et al., 2009).

Collectively, the double impact from the effects of lifestyle changes and breast cancer adjuvant treatment may increase the risk for *late-onset* CVD. Despite this knowledge, there is not a current stratification tool to accurately assess increased risk of CVD morbidity and mortality in breast cancer survivors. For example, sub-clinical cardiac dysfunction may go unnoticed until more overt symptoms occur and still remain undetected by a resting echocardiogram (ECHO) (Cardinale, et al., 2004; Civelli, et al., 2006). However, exercise tests may be more sensitive than resting tests in identifying cardiac dysfunction in long-term survivors (Gottdiener, et al., 1981; Klewer, Goldberg, Donnerstein, Berg, & Hutter, 1992; Weesner, Bledsoe, Chauvenet, & Wofford, 1991).

Therefore, exercise testing may serve as an important clinical tool for identifying breast cancer survivors who are asymptomatic, but at increased risk for the development of CVD. Furthermore, cardiorespiratory exercise testing can provide an objective evaluation of cardiorespiratory fitness, reducing the variability found in self-reported activity measures by 70-80% (Blair & Church, 2004).

While a maximal exercise test is the gold standard for assessing cardiorespiratory fitness, a maximal cardiorespiratory exercise test requires participants to push themselves to volitional exhaustion and peak heart rate (HR) (ACSM, 2009). A maximal effort from the patient is usually confirmed based on various objective and subjective indicators including a; 1) plateau in heart rate and oxygen uptake with increased workload, 2) respiratory exchange ratio > 1.1 , and 3) rating of perceived exertion > 17 (ACSM, 2009). In contrast, submaximal testing allows for an estimated measure of sustainable cardiorespiratory exercise capacity (Wasserman K, Hansen J, & Sue D, 1999). without maximizing heart rate.

Submaximal exercise testing has been used to provide a measure of cardiorespiratory fitness, with outcomes based on an end point at anaerobic threshold or 85% APMHR in patients with a history of congestive heart failure (Kemps, et al., 2008), stroke (Eng, Dawson, & Chu, 2004), cancer (Carlson, Smith, Russell, Fibich, & Whittaker, 2006), and athletic populations (Bernardi, et al., 2010). Although there is not a standard submaximal treadmill protocol, an endpoint at a pre-determined 85% age predicted maximum heart rate may be used (ACSM, 2006; Taylor, et al., 2010).

Submaximal exercise testing is less expensive than maximal testing in that it does not require physician presence during the test, and may be completed without expensive

equipment such as a metabolic cart. Submaximal testing is more feasible for use in de-conditioned women who may discontinue a maximal test early because of fatigue, which is a complaint in 50-80% of breast cancer survivors who have undergone systemic therapy (Andrykowski, Curran, & Lightner, 1998; Gitt, et al., 2002).

A recent meta-analysis indicates a need for a standardized and objective measure of fitness which can be readily utilized in the breast cancer survivorship population (McNeely, et al., 2006). Accordingly, we investigated the association between the gold standard measure of cardiorespiratory fitness (VO_{2max}) with different submaximal testing endpoints in breast cancer survivors. We hypothesized the VO_2 at submaximal endpoints would be highly correlated with VO_{2max} in breast cancer survivors. In addition, we aimed to demonstrate that breast cancer survivors would have a lower VO_{2max} when compared to published normative data. A secondary analysis was to assess left ventricular ejection fraction (LVEF) in breast cancer survivors from measurement with an ECHO or multi gated acquisition scan (MUGA). Important clinical implications can arise from evaluating cardiorespiratory fitness in breast cancer survivors and targeting those in the greatest need of preventive measures.

2.2 Methods

Objectives were to analyze VO_{2max} and submaximal endpoints in breast cancer survivors who had been treated with adjuvant therapy. The submaximal tests utilized a treadmill and an Arc Trainer (Cybex Arc Trainer 750AT) for all cases in this study. Arc Trainers use a low-impact mechanical design with production of lower vertical forces

and joint loading compared to walking on a treadmill (Lu, Chien, & Chen, 2007; Turner, Williams, Williford, & Cordova, 2010).

The study was approved by the University of Kansas Medical Center Human Subjects Committee and written informed consent was obtained from all participants at an orientation meeting prior to conducting any study testing or activities.

Participants

This was a cross-sectional study using a within-subject design to investigate the cardiorespiratory fitness and associations between submaximal and maximal cardiorespiratory tests in breast cancer survivors. A total of 30 breast cancer survivors were enrolled in the study. Recruitment was performed by the recruitment coordinator from follow-up clinics at the University of Kansas Breast Cancer Survivorship Center (BCSC). Inclusion criteria were as follows: previously diagnosed with stage I-IIIa breast cancer; ages 30-60; no evidence of metastatic disease; at least 3-months from completing initial chemotherapy and/or radiation therapy; within 10 years of initial diagnosis; and available results of a resting ECHO or MUGA prior to receiving initial chemotherapy. Subjects had to also have 2 of the following cardiac risk factors: body mass index (BMI) $\geq 25 \text{ kg} \cdot \text{m}^{-2}$, hypertension (systolic blood pressure $\geq 140 \text{ mm Hg}$ and/or diastolic blood pressure $\geq 90 \text{ mm Hg}$) (ACSM, 2009), elevated low density lipoprotein (LDL) (fasting serum level $\geq 130 \text{ mg} \cdot \text{dL}^{-1}$) (NCEP, 2002), positive family history of myocardial infarction, coronary revascularization, or sudden death in mother, father, or first-degree relative, sedentary lifestyle (not currently participating in habitual exercise of moderate to vigorous intensity for two or fewer sessions per week), smoker

(currently smoking or quit smoking within the last six months); and 1 treatment-related risk factor: chemotherapy and/or left breast radiation.

Outcomes

All study procedures were conducted during three testing sessions within a two week time frame at the Clinical Translational Science Unit (CTSU) on the University of Kansas Medical Center campus and the cardiovascular lab located at the University of Kansas Hospital. Participants were instructed to refrain from exercise 48 hours prior to maximal and submaximal cardiorespiratory testing. In addition, all participants were asked not to consume any food, caffeine, alcohol, and tobacco products three hours prior to exercise tests. The exercise testing sessions were between 2 and 14 days apart and at the same time of the day. All cardiorespiratory tests followed the American College of Sports Medicine (ACSM) guidelines for procedures during graded exercise testing (ACSM, 2009). In addition, the exercise testing sessions were at least 48 hours, but no more than 14 days, from the resting ECHO/MUGA. Data on demographic information and health history were obtained (Table 2.1).

Other study measures. Blood pressure and resting heart rate was measured at rest prior to exercise testing. Family history of heart disease, hypertension, low-density lipoproteins, sedentary lifestyle, and smoking habits was assessed from the chart review, clinical interview, and self-report during initial screening for the study.

Maximal treadmill test. Cardiorespiratory fitness was assessed using a modified Balke protocol (Balke B, 1959; Blair, et al., 1989). Tests were conducted by qualified personnel including an exercise physiologist, nurse, and CTSU medical monitor. An

integrated metabolic measurement system (Parvo Medics TrueOne 2400) was used for measurement of maximal oxygen consumption interfaced with an ECG system (Schiller AT-10 Cardiograph). The metabolic cart was set to produce a 15-second average of the data collected during gas analyses for all tests. Equipment was calibrated per manufacturers recommendation prior to testing. Participants were fitted and acclimated to a mouthpiece and headgear (Hans Rudolph; Shawnee, KS) before stepping on to the treadmill. Participants were encouraged to give a maximal effort during the test. The protocol involved 1 minute at 2.0 MPH, 1 minute at 2.7 MPH, and increased to 3.3 MPH and a grade of 1% at minute 3. The grade increased 1% each minute thereafter. Participants continued walking on the treadmill at increasing incline until exhaustion, unless indications for terminating the maximal test were observed (ACSM, 2009). Participants cooled-down at 1.5-2.0 MPH and a level grade for a period of two to five minutes. Expired air was analyzed for O₂ and CO₂. Heart rate, blood pressure, and rating of perceived exertion score were determined at the end of each two minute stage. Confirmation of a maximal effort was determined by meeting three out of four of the following criteria; 1) plateau in heart rate and oxygen uptake with increased workload, 2) respiratory exchange ratio > 1.1, 3) rating of perceived exertion > 17, and 4) heart rate > 90% of age predicted maximal heart rate.

Submaximal treadmill test. Cardiorespiratory fitness submaximal endpoints on the treadmill were determined by the VO₂ at anaerobic threshold and 85% age predicted maximum heart rate. Initial criteria for anaerobic threshold was established by using the respiratory exchange ratio ≥ 1.0 . Participants were allowed to continue for three consecutive 15 second averages at a respiratory exchange ratio ≥ 1.0 to ensure

anaerobic threshold was reached. Post-test confirmation of the anaerobic threshold was made upon visual assessment of 1) V-slope method, and 2) ventilatory equivalent technique to rule out hyperventilation. Submaximal VO_2 at 85% age predicted maximum heart rate was assessed with the calculation $[(220 - \text{age}) \times 0.85]$ and determination of the corresponding VO_2 at that heart rate during maximal testing on the treadmill.

Submaximal Arc (Cybex 750AT) test. After a brief familiarization trial followed by a short rest period, participants began the Arc submaximal test. Participants' weight was input into the console before starting the test. The manual mode was used for testing, with initial workload set at a resistance level of 15. Participants were asked to maintain between 80-100 strides per minute and a level grade was used throughout the test. Workload was adjusted to allow a linear increase in heart rate (5-10 bpm) for each stage until subjects reached the anaerobic threshold endpoint for 3 consecutive 15 second averages. Increased workload was performed manually by a gradual increase in wattage while adjusting resistance in two minute stages. Resistance at each two minute stage varied between participants to allow a steady increase in heart rate, and was adjusted by a 5-10 numerical increase on the Arc trainer console resistance key pad. The cardiorespiratory fitness submaximal endpoint on the Arc trainer was determined by the VO_2 at anaerobic threshold. Criteria for anaerobic threshold was determined by the same method as the submaximal treadmill endpoint.

Cardiorespiratory fitness ($\text{VO}_{2\text{max}}$). Cardiorespiratory fitness was measured by the participants' $\text{VO}_{2\text{max}}$ during the maximal treadmill test. Besides group mean, individual $\text{VO}_{2\text{max}}$ was compared to the normative $\text{VO}_{2\text{max}}$ value for healthy age-matched women.

(2) We performed our maximal treadmill test with a similar Balke protocol that was used for determining normative VO_{2max} values.

Left ventricular ejection fraction. Resting LVEF was performed on all breast cancer survivors by either an ECHO or MUGA, depending on which cardiac function test the participant had prior to starting breast cancer treatment. Resting LVEF at time of study were compared to pre-treatment (baseline) measures. Cardiac function (LVEF) was assessed by a cardiologist not associated with the study.

Anthropometrics and body composition. Body weight was assessed to the nearest 0.1 kg, using an electronic scale (Health o meter, Boca Raton, FI). A stadiometer was used to measure height without shoes to the nearest 0.1 cm (SECA). Body composition was measured by dual-energy x-ray absorptiometry in the total body scanning mode with a Lunar Prodigy DXA machine (Lunar Corp., Madison, WI). Body mass index was calculated as the weight in kilograms divided by the height in meters squared ($kg \cdot m^{-2}$).

Statistical Analysis

Pre-formatted data collection forms and case report forms were used for both clinical and laboratory data. Study data was entered into an Excel data base by a trained data clerk not related to the study. Numbers and percentages were used to describe VO_{2max} in breast cancer survivors compared to age and gender matched normative values. Distribution normality and was verified using the Shapiro-Wilk test and variance homogeneity was confirmed from a Levene's test. After assumptions were met, an association between all submaximal VO_2 endpoints and VO_{2max} was examined using Pearson correlation coefficients. Correlations were categorized as 0.26 to 0.49 is

a low correlation, 0.50 to 0.69 is moderate, 0.70 to 0.89 is high, and 0.90 to 1.00 is very high as described by Munro et al. (Munro, 1993). All analyses were two-tailed with $\alpha = 0.05$, and performed with SPSS statistical software (version 15.0; SPSS Inc, Chicago, IL).

2.3 Results

Participant Characteristics

Participant characteristics and non-treatment CVD risk factors are listed in Table 2.1. Mean age was 50.5 ± 5.6 years, 29/30 were caucasian, 1/30 was Latino, and the group had an average elapsed time since diagnosis of 58 months. The most frequent non-treatment related risk factors were BMI $> 25\text{kg/m}^2$ (83%), elevated LDL (66%), family history of heart disease (40%), and sedentary lifestyle (33%). Additionally, the group mean body fat % was $44.5 \pm 7.7\%$. Treatment related risk factors are listed in Table 2.2 28/30 (93%) of the breast cancer survivors were postmenopausal at time of study, while 20/30 (66%) of the women were treated with an aromatase inhibitor. A large majority (80%) of the women received either doxorubicin or epirubicin, 27% were treated with trastuzumab, and 40% had left chest radiation. Also, the group mean LVEF at time of study was $60.5 \pm 5\%$, which was significantly decreased ($p = 0.02$) from $63.2 \pm 5.7\%$ at time of diagnosis and prior to treatment.

Adverse Events from Testing

All 30 maximal and 30 submaximal cardiorespiratory tests were completed without any adverse events. During maximal testing twenty-eight of thirty participants met our

established criteria for a maximal effort as explained previously. Two of the participants discontinued the test secondary to a claustrophobic sensation related to the mouthpiece, fatigue, and/or shortness of breath. Symptoms were resolved by discontinuing the test and having the participants rest while monitoring all post-test vitals. Even though two participants discontinued the maximal test prior to reaching maximal criteria, both participants achieved > 85% APMHR on the treadmill and have been included in the analyses.

Cardiorespiratory Fitness Levels

Our analysis of cardiorespiratory fitness revealed that 21 out of 30 (70%) women measured below the 20th percentile for their age and gender matched normative VO_{2max} values. When separating into specific age groups, 30-39, 40-49, 50-59, and 60-69 years there were 1/1(100%), 9/12 (75%), 10/15 (66%), and 1/2 (50%) breast cancer survivors respectively that measured below the 20th percentile for VO_{2max} . All submaximal testing of VO_2 endpoints showed a high correlation to the actual measured VO_{2max} when comparing within subject results (Figure 2.1), and the VO_2 at 85% age predicted maximum heart rate on the treadmill showed the highest correlation with VO_{2max} . During our study three participants were unable to complete testing on the Arc trainer due to their inability to coordinate the movement between the lower and upper limbs simultaneously. Also, the Arc trainer produced significantly lower VO_2 ($p < 0.001$) and heart rate ($p = 0.02$) at anaerobic threshold versus the treadmill submaximal test (Table 2.3).

2.4 Discussion

All cardiorespiratory fitness measures are listed in Table 2.3. In this cohort of breast cancer survivors with ≥ 2 risk factors for CVD, 70% had low cardiorespiratory fitness measured by VO_{2max} despite a mean time since diagnosis of over 4 years and a normal LVEF at time of study. These results suggest that they are at a higher risk of breast cancer and cardiovascular mortality (Blair, et al., 1996; Blair, et al., 1995; Peel, et al., 2009). Our results are similar to two earlier reports in breast cancer survivors, (one of which women had controlled hypertension), suggesting the majority of women with non-treatment related CVD risk factors have a lower VO_{2max} compared to healthy women even with a concomitant normal LVEF (Jones, Haykowsky, Pituskin, et al., 2007; Tolentino, et al., 2010). Our study differs from the earlier studies since we used a similar VO_{2max} protocol (Balke protocol) to the standardized treadmill test used for determining normative values rather than a cycle ergometer or Bruce protocol and we reported pre- and post-treatment LVEF.

Sub-maximal exercise testing with VO_2 measured at the anaerobic threshold and 85% APMHR has shown a good correlation with maximal exercise testing in individuals where a maximum test would be difficult because of disability or de-conditioning including those with congestive heart failure, stroke, or undergoing bone marrow transplant (Carlson, et al., 2006; Eng, et al., 2004; Kemps, et al., 2008). To our knowledge, this is the first study to investigate the association between maximal and submaximal cardiorespiratory fitness testing in breast cancer survivors.

The submaximal VO_2 at 85% APMHR was used because this predetermined endpoint could eventually be performed without expensive gas analysis equipment and

can be more feasible than measuring anaerobic threshold when a large number of patients or subjects need to be tested. Overall, the submaximal VO_2 endpoint at 85% APMHR showed the highest correlation to actual measured $\text{VO}_{2\text{max}}$. In addition, the submaximal VO_2 endpoint at 85% APMHR had a similar group mean HR and VO_2 compared to the anaerobic threshold endpoint. This is important to note since anaerobic threshold is a helpful indicator for determining fitness level and for measuring the effect of exercise training (Casaburi, 1994; Casaburi, et al., 1991).

This study suggests that a submaximal test using a modified Balke protocol with an endpoint set at 85% APMHR would be a feasible endpoint to use for a validation study with a maximal test. Therefore, a more practical submaximal test could be performed when the equipment and personnel needed to conduct directly measured oxygen uptake via indirect calorimetry are not available.

We are unaware of previous studies that have used an Arc trainer with decreased load bearing force as an exercise testing modality to examine cardiorespiratory fitness in breast cancer survivors, many of whom have age-related or aromatase inhibitor induced arthralgia and may prefer alternate forms of testing. Turner et al. showed that $\text{VO}_{2\text{max}}$ and time to attain $\text{VO}_{2\text{max}}$ were similar when comparing results between testing modalities including an Arc trainer and a treadmill in healthy adults (Turner, et al., 2010). Overall, we suggest that the benefit of using an Arc trainer does not outweigh difficulty with performing the required coordinated movements and lack of standard testing protocol. Currently, a validated exercise protocol is not available for use on an Arc Trainer. Also, It is important to note that there were no breast cancer survivors in our study that could not complete testing on the treadmill due to joint or muscle pain.

2.5 Conclusion

This is the first study to investigate the association between the gold standard for cardiorespiratory fitness (VO_{2max}) to submaximal VO_2 tests in breast cancer survivors who had been treated with adjuvant therapy. The findings from this study indicate that the majority (70%) of breast cancer survivors with ≥ 2 CVD risk factors had low cardiorespiratory fitness and submaximal testing on the treadmill is a feasible, objective measure of fitness that can be used in breast cancer survivors. A main limitation of this study included the sample size ($n= 30$), which was too small for a validation study. In addition our sample lacked racial diversity and a control group.

Future research should include a large enough group of breast cancer survivors for a study to validate a submaximal test. Since our study indicated the 85% APMHR had the highest correlation, a future study aimed at validating the use of this submaximal endpoint to a maximal test would be helpful. Rather than using healthy age predicted normal values, women who share similar CVD risk factors and are at high-risk for breast cancer but have not received treatment may be a more appropriate comparison group to investigate the effects of breast cancer treatment on cardiorespiratory fitness. In addition, novel approaches should be made to improve cardiorespiratory fitness during sustainable exercise interventions for breast cancer survivors.

Tables and Figures

Table 2.1 Participant Demographics and Non-Treatment Related Characteristics

Variable	Breast Cancer Survivors (<i>n</i> = 30)
Age (y)	50.5 ± 5.6
Time since diagnosis (months)	58 ± 27
BMI (kg·m ⁻²)	29.2 ± 5.3
Body fat (%)	44.5 ± 7.7
Overweight (BMI > 25 kg·m ⁻²)	25/30 (83%)
Hypertension	8/30 (27%)
↑ LDL	20/30 (66%)
Family history heart disease	12/30 (40%)
Sedentary lifestyle	10/30 (33%)
Smoker	1/30 (3%)

Note: BMI, body mass index; LDL, low density lipoprotein.

Table 2.2 Treatment Related Characteristics

Variable	Breast Cancer Survivors (<i>n</i> = 30)
Current Aromatase Inhibitor	14/30 (47%)
Current Tamoxifen	1/30 (3%)
Past AI's	4/30 (13%)
Past Tamoxifen	1/30 (3%)
Post-menopausal	28/30 (93%)
Adriamycin/Epirubicin	24/30 (80%)
Herceptin	8/30 (27%)
Left chest radiation	12/30 (40%)

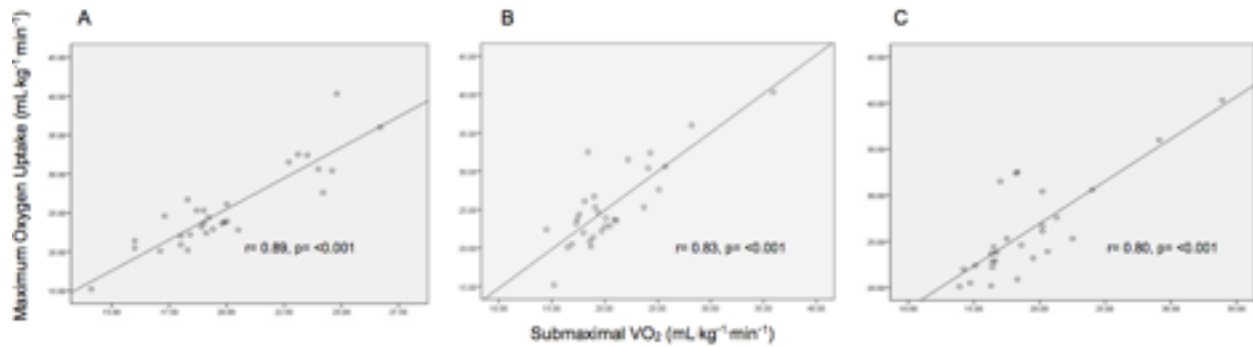
Table 2.3 Cardiorespiratory Outcomes

Variable	Breast Cancer Survivors (<i>n</i> = 30)
Maximal VO ₂ (mL·kg ⁻¹ ·min ⁻¹)	25.4 ± 5.3
Maximal HR (bpm)	169 ± 12
VO ₂ at AT on treadmill (mL·kg ⁻¹ ·min ⁻¹)	20.5 ± 4.3
VO ₂ at AT on Arc (mL·kg ⁻¹ ·min ⁻¹)	19.0 ± 4.4
VO ₂ at 85% APMHR (mL·kg ⁻¹ ·min ⁻¹)	19.9 ± 3.0
HR at AT on treadmill (bpm)	148 ± 13
HR at AT on Arc (bpm)	144 ± 13
HR at 85% APMHR (bpm)	144 ± 5
Predicted Maximal HR (bpm)	170 ± 6
Predicted VO ₂ - 85% APMHR (mL·kg ⁻¹ ·min ⁻¹)	24.5 ± 7.2
Predicted VO _{2max} (mL·kg ⁻¹ ·min ⁻¹)	34.5 ± 8.8
Resting HR (bpm)	78 ± 10
Maximal O ₂ pulse (mL/beat)	11.5 ± 1.5
Pre-Treatment LVEF	63.2 ± 5.7%
Study LVEF	60.5 ± 5.0%

Note: HR, heart rate; AT, anaerobic threshold; APMHR, age predicted maximal heart rate; LVEF, left ventricular ejection fraction.

Figure 2.1 Association Between Submaximal and Maximal VO_2

The association between maximal oxygen uptake with (A) treadmill 85% APMHR endpoint, (B) treadmill AT endpoint, and (C) Arc trainer AT endpoint.



Chapter 3

*Cardiovascular Exercise Dose Intensity for Improving Cardiorespiratory Fitness
in Breast Cancer Survivors*

3.1 Introduction

Early diagnosis and adjuvant therapies have been effective at increasing women's life span after breast cancer diagnosis. It is estimated that greater than 75% of breast cancer survivors will live ten years after diagnosis (NCI, SEER 1996-2007) and the number of breast cancer survivors exceeds 2.5 million (ACS, 2012). With this increased survival, many women may suffer from long-term effects of their diagnosis and treatment. Evidence shows that in addition to risk for recurrence, cancer survivors are at a greater risk than their non-cancer peers for developing secondary tumors and cardiovascular disease (CVD) (Demark-Wahnefried & Jones, 2008). Furthermore, a recent study suggested that the 10 year CVD risk estimate may exceed that of breast cancer recurrence (Bardia, et al., 2012); and showed that 80% of breast cancer survivors had a predicted CVD risk that was equal or greater than the breast cancer recurrence risk (Bardia, et al., 2012).

It has been established that the treatment of breast cancer (adjuvant therapy, radiation, hormone therapy) may directly increase the risk of cardiac dysfunction (ASCO, 2007). In addition to these direct effects of treatment, the physical inactivity and weight gain may play an indirect role in cardiac dysfunction as well. Breast cancer survivors have reported decreasing their activity by an average of two hours per week or more based on their treatment regimen (Irwin, et al., 2003). Women with low cardiorespiratory fitness are at increased risk for all-cause mortality (Blair, et al., 1989) and breast cancer mortality (Peel, et al., 2009). A previous study demonstrated that the greatest impairment in cardiorespiratory fitness was associated with a worse CVD risk profile in breast cancer patients (Jones, Haykowsky, Pituskin, et al., 2007). However,

there is a paucity of data available for the effects of exercise training aimed at improving cardiorespiratory fitness, and ultimately, modifying CVD risk factors in breast cancer survivors.

To further exacerbate the likelihood for poorer health outcomes, weight gain can result from adjuvant treatment for breast cancer or physical inactivity. Weight gain in breast cancer survivors has shown to significantly increase CVD mortality (Nichols, et al., 2009), with a 19% increase in CVD mortality associated with each 5-kg gain in weight after breast cancer. In addition, breast cancer survivors with a body mass index (BMI) greater than 25 kg/m² have up to a 60% increased risk for death compared to survivors with normal body weight (Saxton, et al., 2006). A sedentary lifestyle can be seen as a precursor for the build-up of visceral fat, leading to an additional risk for CVD and tumorigenesis (Bird & Swain, 2008; Pedersen, 2009). Therefore, the potential for diet and exercise interventions to have a positive effect on targeted health outcomes in breast cancer survivors may have implications for long-term survival.

A few studies have demonstrated that physical activity interventions have been successful at improving cardiorespiratory fitness in breast cancer survivors (McNeely, et al., 2006; K. H. Schmitz, Holtzman, et al., 2005), and a recent review indicated that exercise interventions can improve fitness, physical function, and strength (Pekmezi & Demark-Wahnefried, 2011), while diet interventions can improve body weight, diet quality, and nutrition-related biomarkers (Pekmezi & Demark-Wahnefried, 2011). Furthermore, evidence points to a significant survival advantage for breast cancer survivors who engage in combined diet and exercise behavioral change versus exercise or diet alone (Pierce, et al., 2007). However, the cost of monitored and supervised

interventions and the demands on time and travel for cancer survivors are significant barriers to the implementation of these interventions (Pekmezi & Demark-Wahnefried, 2011). Thus, there is a need to investigate home-based lifestyle interventions for cancer survivors as they may be more sustainable and applicable to the growing cancer survivor population.

Diet and physical activity guidelines targeting cancer survivors have been issued by the American Cancer Society (ACS) and American College of Sports Medicine (ACSM) (Doyle, et al., 2006; K. H. Schmitz, et al., 2010). Despite these guidelines additional exercise trials are needed to explore the effects of different exercise prescriptions and dosing intensity (Neilson, et al., 2009). Additionally, more evidence is needed on the effects exercise interventions have on targeted outcomes of greatest need in cancer survivors. The purpose of our study was to investigate the effects of different cardiovascular dose intensities during a home-based diet and exercise intervention on targeted CVD and breast cancer risk factors in breast cancer survivors. Subjects participated in two different dose intensities, moderate continuous training (MCT) and interval training (IT). First, we hypothesized that breast cancer survivors would be able to adhere to MCT and IT during a home-based intervention. Specifically, we predicted that participants in both groups would achieve > 75% of their weekly prescribed cardiovascular exercise, without significant adverse events. Second, we hypothesized that IT would elicit greater improvements on selected CVD and breast cancer risk factors including weight loss and increased cardiorespiratory fitness (VO_{2max}) versus MCT in breast cancer survivors. Lastly, we explored associations

between change in $VO_{2\max}$ to exercise time and intensity (average HR) downloaded from the HR monitors.

3.2 Methods

Study Design. This study used a cross-sectional design for baseline comparisons and within- and between-group design for analyzing repeated measures after an intervention. Participants were enrolled into two treatment groups receiving different levels of cardiovascular exercise dosing intensity, as depicted in Figure 3.1. The study was conducted at the University of Kansas Medical Center (KUMC). The Human Subjects Committee at KUMC approved all study procedures. Written informed consent was obtained from all participants at an orientation meeting prior to conducting any study testing or activities.

Recruitment and participants. A convenience sample of 19 women was recruited from the University of Kansas Breast Cancer Survivorship Center (BCSC) between November 2010 and October 2011. Recruitment was completed in two waves and performed by the recruitment coordinator from follow-up clinics at the BCSC. Flow of participants through the study is provided in Figure 3.2. The recruitment coordinator performed a chart review on patients currently enrolled in the BCSC data base to identify eligibility and placed a phone call to enroll participants into the study. The first group started the intervention in March 2011 and finished in July 2011, while the second group began in October 2011 and finished in February 2012. The first group ($n=12$) received moderate continuous training (MCT) and the second group ($n=7$) was prescribed a higher intensity of cardiovascular exercise using interval training (IT).

Study personnel obtained written permission from participants' treating oncologist to perform all testing, diet, and exercise components of the intervention. To assess participants ability to safely perform exercise, a health history form was administered to all participants. A lymphedema risk assessment self-care questionnaire and the Norman Lymphedema Survey was administered to all participants during initial screening to further rule-out possible diagnosis of lymphedema.

Eligibility requirements included that participants had to: 1) be approved for participation in a diet and exercise program by their treating clinician, 2) have completed any intravenous therapy (chemotherapy) or radiation for ≥ 8 weeks before starting the intervention, 3) have no evidence of metastatic disease, 4) be within 3 years of diagnosis of breast cancer and if on anti-hormonal therapy must have been on therapy for ≥ 6 months, 4) be between ages 25-70, 5) have a BMI of 25-45 kg/m², 6) be reasonably healthy with no medical conditions limiting trial participation, 7) be willing to participate in a structured diet/exercise/behavioral program requiring weekly group meetings in person, and 8) be at high risk for lymphedema (≥ 5 lymph nodes removed), with no history of lymphedema. Participants were excluded from the study if they met one of the following criteria: 1) breast cancer staged higher than IIIa, 2) medical status that would preclude safety of participation in a weight loss and exercise program, 3) on cardiac medications that would effect cardiac function, or 4) already enrolled in a weight loss program.

Diet and Exercise Intervention

Resistance Training Education. An exercise physiologist met with participants 2 times per week during the first month (weeks 1-4) of the intervention in groups of 2-6 survivors to teach participants how to safely and effectively perform the resistance exercises, as seen in Figure 3.1. This education program was aimed at equipping the participants with the proper resistance training technique and form before starting training at home during week 5; and not on weight training. Adjustable weight dumbbells (PowerBlock, Owatonna, MN) were provided to the participants for the home-based intervention. Throughout weeks 1-4 all participants were taught proper form and technique for 2-4 resistance training exercises during each of the 8 visits. ROM and/or light weight (1-2 pounds) was used to effectively perform 15 repetitions with proper technique during the 1 month resistance education. Specific stretching exercises were taught to all participants for the purpose of warming-up and decreasing chance of injury prior to the resistance training. After stretching, all participants learned the proper technique for 3 core strengthening exercises to improve lower back and trunk stabilization that they would use when beginning the resistance training. Starting at week five all participants began the diet, combined exercise training (resistance/ cardiovascular), and weekly group meetings.

Resistance Training Exercise. During weeks 5-8 all participants were instructed to perform 2 sets of 15 repetitions of each resistance exercise. Once 15 repetitions for 2 sets was completed with proper technique and form for 2 consecutive resistance training sessions, participants increased weight. Weight was increased by 10% or 1 pound, whichever was the least amount. Participants added a 3rd set of 15 repetitions

during weeks 9-17, as long as they could successfully complete their current weight for 15 repetitions with safe technique. When participants were able to complete 3 sets of 15 repetitions they could increase weight in small increments as previously described. Correct weight was selected to complete all repetitions with safe and proper technique. A second bout of stretching exercises concluded each resistance training session. A packet with pictures and order of all resistance, stretching, and core exercises was provided to all participants.

Behavioral modification. All study participants took part in a behavioral modification program starting at week 5. Weekly one-hour sessions providing a group support system that facilitates weight loss included topics on nutrition, breast cancer and lifestyle, psychosocial issues and weight reduction. Sessions were led by a registered dietitian, clinical health psychologist, and an exercise physiologist who were trained to deliver the behavioral modification program. All sessions were delivered with pre-formatted print and visual materials. Participants were required to maintain a weekly diet and exercise log and weigh-in at each session. The diet consisted of 1200-1500 calories per day. Daily recommendations consisted of 2 prepackaged meals (any brand <350 calories, <10g fat per meal) and 2 high whey-protein shakes (~150-180 calories, 10g protein) participants purchased from their local grocery store, and >5 fruit and vegetable servings daily.

Cardiovascular Training Exercise: Cardiovascular exercise was delivered in the form of moderate continuous training (MCT) or interval training (IT). Participants in both groups were provided with, and instructed on the use of, a Garmin HR monitor (FR60)

to use during all cardiovascular exercise sessions. The exercise time and HR data was periodically downloaded for analysis by the exercise physiologist.

(MCT). After four weeks of resistance education, participants in this group were instructed in a moderate intensity walking or exercise program. A moderate exercise intensity was described as, 'very easy to carry on a conversation while exercising'. This program was prescribed according to "usual care" as delivered by our oncology medical team. Therefore, no specific heart rate (HR) was prescribed. Cardiovascular exercise included walking outside, on a treadmill, cycle ergometer, or other activities. In addition, participants were prescribed a progressive increase in cardiovascular exercise minutes, starting at week 5 with 60 minutes and progressing to 75, 90, and 150 minutes of cardiovascular exercise during weeks 7, 10, and 14, respectively. A minimum of 20 minutes per exercise session was encouraged.

(IT). Participants in the IT group were prescribed the same moderate exercise intensity with the same number of exercise minutes per week as the MCT group during weeks 5-8, as seen in Figure 3.1. At the beginning of week 9 participants in the IT group were provided an individually prescribed new target HR range to use during IT bouts. The prescriptions were based on a HR range equal to 85-95% of the maximal HR achieved during the baseline cardiorespiratory fitness test (described in outcome measures below). Participants in the IT group were instructed to incorporate an IT bout into their cardiovascular exercise sessions as described in Table 3.1. Overall, time spent in the IT dose intensity was between 30

seconds to 5 minutes per interval and 2 minutes to 15 minutes per session (Table 3.1).

Outcomes

All baseline and 17-week outcomes were performed by the same testing staff on the same equipment. Measurement staff used scripts or were blinded to avoid biasing of results.

Maximal Cardiorespiratory Fitness (VO_{2max}). Cardiorespiratory fitness was assessed using a modified Balke protocol (Balke B, 1959; Blair, et al., 1989). Tests were conducted by qualified personnel including an exercise physiologist, nurse, and medical monitor. An integrated metabolic measurement system (Parvo Medics TrueOne 2400) was used for measurement of maximal oxygen consumption interfaced with an ECG system (Schiller AT-10 Cardiograph). The metabolic cart was set to produce a 15-second average of the data collected during gas analyses for all tests. Equipment was calibrated per manufacturers recommendation prior to testing. Blood pressure and resting HR was measured at rest prior to exercise testing. Participants were fitted and acclimated to a mouthpiece and headgear (Hans Rudolph; Shawnee, KS) before entering the treadmill. Participants were encouraged to give a maximal effort during the test. The protocol involved 1 minute at 2.0 MPH, 1 minute at 2.7 MPH, and increased to 3.3 MPH and a grade of 1% at minute 3. The grade increased 1% each minute thereafter. Participants continued walking on the treadmill at increasing incline until exhaustion, unless indications for terminating the maximal test were observed (ACSM, 2009). Participants cooled-down at 1.5-2.0 MPH and a level grade for a period of two to

five minutes. Expired air was analyzed for O₂ and CO₂. Heart rate, VO₂, blood pressure, and RPE score were determined at the end of each stage. Confirmation of a maximal effort was determined by meeting three out of four of the following criteria; 1) plateau in heart HR and oxygen uptake with increased workload, 2) respiratory exchange ratio (RER) > 1.1, 3) rating of perceived exertion (RPE) > 17, and 4) HR > 90% of age predicted maximal HR.

Body composition. Body weight was assessed to the nearest 0.1 kg, using an electronic scale (Health o meter, Boca Raton, FL). A stadiometer was used to measure height without shoes to the nearest 0.1 cm (SECA). Body composition was measured by dual-energy x-ray absorptiometry in the total body scanning mode with a Lunar Prodigy DXA machine (Lunar Corp., Madison, WI). Body mass index was calculated as the weight in kilograms divided by the height in meters squared (kg·m⁻²).

Exercise adherence, exercise minutes, and exercise intensity. Participants turned-in exercise logs during the weekly group meetings. If the exercise log was not turned in, the study coordinator contacted the participant by e-mail to remind them to send the log to the BCSC or bring to the next weekly group meeting. The exercise log included type of exercise, minutes spent on resistance training, minutes spent cardiovascular training, and any narrative for adverse events. Additionally, cardiovascular exercise time and intensity (heart rate) were collected by downloading each participants cardiovascular exercise data from their heart rate monitor on a periodic basis throughout the intervention.

Adverse events. Adverse events were collected during the intervention, as described by the NCI Common Toxicity Criteria, (version 4.2). Participants were

instructed to call the study coordinator if any adverse events occurred, regardless of whether the event was related to the study. In addition, the study coordinator asked participants, at weekly sessions, if any adverse events occurred during the previous week.

Statistical Analysis

Baseline characteristics of participants were compared between the two treatment groups using Student's *t*-tests for continuous variables and Pearson's Chi-square tests for categorical variables. Normality of outcomes was verified using the Shapiro-Wilk test and variance homogeneity was confirmed from a Levene's test prior to analyzing baseline characteristics and within- and between-group comparisons. Due to a small sample size, non-parametric testing was used in some variables where normal distribution did not occur or unequal variance was present. Mann-Whitney U tests were substituted if assumptions for the *t*-test were violated or unable to be verified. All analyses were two-tailed with $\alpha = 0.05$ and performed with SPSS statistical software (version 15.0; SPSS Inc, Chicago, IL).

Exercise adherence was determined by average weekly exercise time achieved for the IT and MCT groups during the intervention. Subjects achieving greater than 75% of the prescribed time were considered adherent. Descriptive statistics including frequencies and percentages for categorical variables and means and standard deviations for continuous variables were used to report exercise adherence. Differences in the rate of adherence between groups were assessed using a chi-square test. Additionally, self-reported cardiovascular training time, self-reported resistance

training time, average HR from Garmin data, cardiovascular training time from Garmin data, and nutritional intake (number of prepackaged meals, shakes, fruits and vegetables) were compared between groups using Student's *t*-tests.

Changes in body composition (weight, BMI, % fat mass, absolute fat mass, absolute lean mass) and cardiorespiratory fitness (VO_{2max}) were tested for significance using paired Student's *t*-tests. Wilcoxon signed ranks tests were substituted when assumptions for the *t*-test were violated or unable to be verified.

Comparisons were also made between the changes in body composition (weight, BMI, %fat mass, absolute fat mass, absolute lean mass) and cardiorespiratory fitness (VO_{2max}) for participants in the IT group versus those in the MCT group. Again, two-sample Student's *t*-tests were used to identify significant differences in outcome measures. Mann-Whitney U tests were used if any assumptions were violated or unable to be verified.

Lastly, to explore if cardiovascular exercise dose intensity was associated with changes in VO_{2max} , we analyzed cardiovascular exercise time and intensity downloaded from a heart rate monitor. Pearson correlation coefficients were used to assess bivariate associations between change in VO_{2max} and cardiovascular exercise outcome variables from the heart rate monitor data (average HR and time).

Normality of outcomes was verified using the Shapiro-Wilk test and variance homogeneity was confirmed from a Levene's test prior to analyzing baseline characteristics and within- and between-group comparisons. All analyses were two-tailed with $\alpha = 0.05$ and performed with SPSS statistical software (version 15.0; SPSS Inc, Chicago, IL).

3.3 Results

Figure 3.2 is a CONSORT diagram showing that 12 participants were enrolled into the MCT group and 7 into the IT group. Reasons for loss to follow-up included personal issues ($n = 2$) and flare-up of lymphedema ($n = 1$). One of the two participants with personal issues was able to complete part of the follow-up testing, but was unable to schedule cardiorespiratory fitness testing. All three participants without complete follow-up test results were from the MCT group.

Table 3.2 describes the baseline characteristics of the 17 participants who completed pre- and post-intervention testing. No significant differences were noted in any baseline variables between groups. All women were post-menopausal at time of study and received chemotherapy and/or radiation during treatment. In addition, all women were currently taking tamoxifen or an aromatase inhibitor (AI) at time of study.

Maximal Cardiorespiratory Fitness (VO_{2max}). All participants were able to meet 3 out of four criteria for achieving a maximal test at both time points. The IT group had a significantly greater increase for VO_{2max} ($p = 0.05$) and duration on treadmill ($p = 0.02$) compared to the MCT group, as shown in Table 3.3. No significant between-group differences were noted for all other cardiorespiratory fitness testing outcomes. As seen in Table 3.3, significant within-group changes were noted for both groups in cardiorespiratory fitness testing measures including VO_{2max} and duration on treadmill. Also, Table 3.3 indicates the P values for comparison of changes between the MCT and IT groups. Furthermore, analyses of individual change for VO_{2max} for all participants are shown in Figure 3.3. The dotted line in Figure 3.3 represents a threshold VO_{2max} of

28 mL·kg⁻¹·min⁻¹. Peel et al. showed an approximate 2.5 fold increase in death from breast cancer occurred in women with a previously measured cardiorespiratory fitness capacity below 8 METS, equal to a $VO_{2max} < 28 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ [1 metabolic equivalent (MET) = 3.5 mL·kg⁻¹·min⁻¹] (Peel, et al., 2009). All participants in the IT group experienced an improvement in their VO_{2max} . However, two participants in the MCT group had a 17 week $VO_{2max} \leq$ their baseline measure.

Body composition. Table 3.4 shows the within- and between-group changes over the diet and exercise intervention for body composition. The results indicate there were significant changes across groups for all major body composition measures, except absolute lean mass (Table 3.4). Further analyses showed there were no significant between-group differences for change in body composition measures.

Exercise adherence, exercise minutes, and exercise intensity. Self-reported adherence to the prescribed diet and exercise intervention was assessed from weekly diet and exercise logs, as seen in Table 3.5. The primary adherence outcome measure was defined as the number of participants in both groups who achieved > 75% of their weekly prescribed cardiovascular exercise. Both groups achieved > 75% of prescribed cardiovascular exercise time for each of the 13 weeks during the combined diet and exercise intervention, identified by self-report weekly logs. Adherence to the prescribed diet was similar in both groups, except for a significant difference between the MCT and IT groups in the average number of fruits and vegetables consumed each week ($p < 0.01$). Furthermore, total cardiovascular training time and average HR were analyzed from data downloaded from the HR monitors. Total cardiovascular exercise time retrieved from the HR monitor compared to self-reports for the MCT and IT groups was

76% and 90% respectively. Downloaded cardiovascular exercise training time (average of total minutes per participant) was similar between the MCT and IT groups. However, cardiovascular training average HR was significantly higher for the IT group versus to the MCT ($p = 0.03$), as seen in Table 3.5.

Explorative analyses for associations between change in VO_{2max} with cardiovascular exercise intensity (average HR) and time downloaded from the HR monitors were performed, as shown in Figures 3.4 and 3.5, respectively. Results indicated the IT group showed a significant ($p < 0.05$) and high correlation ($r = 0.82$) between VO_{2max} with average HR, but not exercise time. No significant correlations were noted within the MCT group when analyzing association between VO_{2max} and cardiovascular exercise time or average HR.

Adverse events. Four participants in the MCT group and one in the IT group had AE's unrelated to the study. All AE's were identified as ≤ 2 on a severity scale of 1-4, as described by the NCI Common Toxicity Criteria, (version 4.2). The only patient with an AE related to study procedures was a participant in the IT group who had asymptomatic premature ventricular contractions (PVC's) during her baseline maximal cardiorespiratory exercise test. Follow-up was made with an onco-cardiologist to rule-out any significant coronary artery disease.

3.4 Discussion

To our knowledge, this is the first study to evaluate the effects of exercise dosing on CVD and breast cancer risk factors during a home-based diet and exercise intervention for breast cancer survivors. We found that both groups were able to

significantly improve body composition (weight, BMI, % body fat) and VO_{2max} while adhering to their prescribed exercise time. Home-based interventions may favor sustainability versus strictly supervised programs (Pekmezi & Demark-Wahnefried, 2011). Lifestyle change may be achieved as breast cancer survivors modify their behavior in an independent fashion during a home-based intervention. In addition, combined diet and exercise interventions can provide a meaningful survival advantage compared to diet or exercise alone (Pierce, et al., 2007). Our findings suggest that exercise dosing is feasible to prescribe in a home-based program using a combined diet and exercise intervention; and can have a positive impact on breast cancer and CVD risk factors including VO_{2max} and weight loss and in breast cancer survivors.

The individual effect of diet and exercise alone must be considered when assessing the improvement of VO_{2max} after combined interventions. Specific to our study, we must use caution when associating improved VO_{2max} with cardiovascular exercise dosing without considering the impact a calorie restricted diet may have on improvement in cardiorespiratory fitness. Studies have assessed the improvement in VO_{2max} when comparing diet or exercise alone versus diet plus exercise. In a recent 12-week randomized intervention, obese participants were randomized to exercise only, calorie restriction only, or exercise and calorie restriction. The results indicated a significant increase in VO_{2max} from the exercise alone or the combined exercise and calorie restriction intervention (14% and 18%, respectively), but found no change in VO_{2max} in the calorie restriction alone group (Christiansen, et al., 2010). In a similar 6-month intervention in overweight (non-cancer) participants, caloric restriction only versus caloric restriction plus aerobic exercise versus weight maintenance diet, VO_{2max}

significantly improved (increased) in the caloric restriction plus aerobic exercise arm only, 22+/-5% vs 7+/-5% (caloric restriction alone), vs -5+/-3% (weight maintenance diet) (Larson-Meyer, et al., 2010). Overall, interventions targeting cardiorespiratory fitness without exercise are not likely to significantly improve VO_{2max} .

To examine the effects cardiovascular exercise dose intensity has on CVD and breast cancer risk factors, we compared changes in VO_{2max} and body composition between the MCT and IT groups. Our study showed a significant greater mean increase in change for both VO_{2max} and duration on treadmill for the IT group when compared to the MCT group pre- to post-intervention. There were no further significant mean differences in change for CVD and breast cancer risk factors between the MCT and IT groups. Therefore, our study suggests that a group prescribed IT can improve VO_{2max} significantly more than MCT during a home-based intervention for breast cancer survivors.

Clinical implications stem from improving VO_{2max} , since increased cardiorespiratory fitness (measured as VO_{2max}) has been associated with a decrease in all-cause mortality and CVD in apparently healthy men and women. Each one metabolic equivalent [1 metabolic equivalent (MET) = $3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$] increase in VO_{2max} corresponded to an 11-13% and 15-18% reduction of all-cause mortality and CVD respectively (Barlow, et al., 2012; Kodama, et al., 2009). In our study, the IT group experienced a $5.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ improvement, while the MCT saw a significantly lower improvement in VO_{2max} at $2.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Based on these previous results of Barlow et al. and Kodama et al., both groups were able to reduce their risk for all-cause mortality and CVD. Furthermore, our study led to significant improvements in cardiorespiratory

fitness for breast cancer survivors who are an increased risk for all-cause mortality and CVD compared to their non-cancer age matched peers.

Previous studies indicate that a low predicted VO_{2max} increases risk for CVD occurrence (Blair, et al., 1996) and breast cancer mortality (Peel, et al., 2009). Cardiorespiratory fitness was measured in a large group of healthy women. A linear trend ($p = 0.007$) was noted for an inverse relationship between breast cancer mortality and cardiorespiratory fitness (Peel, et al., 2009). Another study by Sui et al. determined a linear trend ($p = 0.03$) for CVD incidence based on cardiorespiratory fitness in women with at least 2 CVD risk factors (Sui, LaMonte, & Blair, 2007). In Sui's study there was an inverse relationship between predicted VO_{2max} from a maximal treadmill test and CVD incidence. Based on these previous studies our findings may have implications for IT to improve a major CVD and breast cancer risk factor $\sim VO_{2max}$. Additionally, results from this study indicate that prescribing IT may be safe and feasible in a home-based diet and exercise intervention. Specifically, the IT group was able to perform cardiovascular exercise at a significantly higher average HR compared to the MCT group without experiencing any AE's related to the prescribed exercise intensity.

It has been suggested that IT above 85% VO_{2max} can contribute to both aerobic and anaerobic metabolic adaptations leading to more pronounced improvement of VO_{2max} versus moderate intensity continuous exercise (Butcher & Jones, 2006; Cornish, et al., 2010; McArdle, 2007; Poole & Gaesser, 1985; Tabata, et al., 1996). Furthermore, IT at higher intensities has shown to be superior to continuous training at moderate levels for improving VO_{2max} with sedentary (Daussin, et al., 2008), chronic obstructive pulmonary disease (Butcher & Jones, 2006), CAD (Cornish, et al., 2010), and athletic

(McArdle, 2007) populations. Even though we were not able to assess the proportion of time individuals spent within their prescribed IT intensity, our study indicated that exercise intensity (average HR) had a high correlation to an increase in VO_{2max} within the IT group.

Adherence was similar across groups for all diet and exercise variables measured by self-report, except for the amount of fruits and vegetables consumed. Additionally, both groups had similar total cardiovascular exercise time as measured by heart rate monitors. However, the IT group showed a significant greater average HR during cardiovascular exercise training when compared to the MCT group, measured by heart rate monitors. Explanations for the significantly higher HR may include the differing cardiovascular exercise prescription favoring a higher target HR in the IT group.

This study has two main limitations. A larger sample size and a randomized controlled design will help determine the effects of cardiovascular exercise dosing. Our future work will include a larger sample size and a randomized design so that meaningful comparisons can be made between the MCT and IT groups for outcomes related to body composition and cardiorespiratory fitness. Therefore, the results from this study may provide the groundwork for additional trials. Future exercise interventions in breast cancer survivors should include cardiovascular exercise dose intensity to help establish the effectiveness of IT on cardiorespiratory fitness. Further sophisticated analysis of heart rate during IT bouts should be performed in order to more precisely evaluate time spent in the prescribed IT heart rate zone. If we can quantify the proportion of time participants exercise in their prescribed IT heart rate zone, we may conclude that prescribed IT heart rate zones are adhered to. Therefore, providing us a

more robust conclusion on IT's association to improving VO_{2max} greater than MCT. A larger multi-center randomized controlled trial will be useful for determining exercise intensity dosing impact on breast cancer survivors in a home-based intervention. Also, it can be useful to increase the time of the RCT and include a long-term follow-up phase to assess sustained lifestyle change. Finally, 5-10 year longitudinal studies are needed to investigate the effect of a combined diet and exercise home-based intervention on CVD and secondary breast cancer risk. More work is needed in order to establish the optimal exercise dose to elicit the greatest improvement in CVD and breast cancer risk factors in breast cancer survivors.

3.5 Conclusion

In conclusion, the IT group was able to produce a higher average heart rate versus the MCT group during their prescribed cardiovascular exercise. In addition, increased change in VO_{2max} was significantly correlated with average heart rate during cardiovascular exercise in the IT. Prescribing cardiovascular exercise dosing during a home-based diet and exercise intervention appears to be feasible and safe for breast cancer survivors. Additionally, the IT group produced significantly greater mean change in VO_{2max} than the MCT group during our study. Including IT into exercise and rehabilitation programs may promote improvements in cardiorespiratory fitness, while decreasing the risk of CVD and possibly breast cancer recurrence. This study highlights the need for future research to examine the effect exercise dosing has on CVD and breast cancer risk factors including weight loss and VO_{2max} on a large sample of breast cancer survivors.

Table 3.1 Interval Training Prescription Timeline

Timeline	Cardiovascular Exercise Intensity Dose
Weeks: 5-8	Usual care moderate exercise
Weeks: 9-10	<ul style="list-style-type: none"> • IT Bout: 30 seconds to 1 minute • Total IT time: 2-3 minutes per 20 minutes cardiovascular exercise
Weeks: 11-12	<ul style="list-style-type: none"> • IT Bout: 30 seconds to 2 minutes • Total IT time: 3-4 minutes per 20 minutes cardiovascular exercise
Weeks: 13-17	<ul style="list-style-type: none"> • IT Bout: 1 to 5 minutes • Total IT time: 4-5 minutes per 20 minutes cardiovascular exercise

Participants were instructed to perform between 20-60 minutes per exercise bout. Recovery between intervals must have been 2x the length of the interval.

Table 3.2 Baseline Characteristics of Breast Cancer Survivors
[Mean (SD) or *n* (%)]

Variable	MCT (<i>n</i> = 10)	IT (<i>n</i> = 7)	<i>P</i>
Age (years)	53 (11.3)	52 (6.3)	0.48 [^]
Ethnicity	10 (100%)	6 (86%)	0.22 ^{^^}
Time since diagnosis (months)	21.2 (7.6)	23.7 (12.2)	0.61
Activity level (exercise minutes)	99.5 (122.3)	146.4 (125.5)	0.89 [^]
Post-menopausal	10 (100%)	7 (100%)	0.99 ^{^^}
Left-chest radiation	4 (40%)	3 (43%)	0.91 ^{^^}
Chemotherapy	7 (70%)	4 (57%)	0.59 ^{^^}
Hormone blocker	10 (100%)	6 (86%)	0.22 ^{^^}
Cardiac Risk Factors (average)	2.3	2.0	0.44
Weight (pounds)	196.7 (39.9)	183.9 (15.3)	0.67 [^]
BMI (kg·m ⁻²)	33.3 (6)	31.1 (4.4)	0.42
Fat mass (%)	48.6 (6.5)	45.7 (5.9)	0.35
VO _{2max} (mL·kg ⁻¹ ·min ⁻¹)	24.0 (7.1)	24.6 (2.9)	0.85
Treadmill duration (seconds)	677.2 (319.6)	794.0 (131.3)	0.61 [^]

[^] Mann-Whitney U test

^{^^} Pearson Chi-square test

Table 3.3 Cardiorespiratory Fitness Pre- and Post-Intervention [Mean (SD)]

Variable	Pre MCT (<i>n</i> = 10) IT (<i>n</i> = 7)	Post MCT (<i>n</i> = 9) IT (<i>n</i> = 7)	Change	<i>P</i> for within group change	<i>P</i> for between group change
VO _{2max} (mL.kg ⁻¹ .min ⁻¹)					
MCT Group	24.0 (7.1)	26.3 (6.8)	2.3 (2.9)	0.05 [*]	0.05 [*]
IT Group	24.6 (2.9)	29.8 (3.8)	5.3 (2.6)	0.002 ^{**}	
Treadmill Duration (seconds) (at VO _{2max})					
MCT Group	677.2 (319.6)	813.7 (271.2)	136.4 (101.9)	0.02 ^{**}	0.02 ^{**} ^
IT Group	794.0 (131.3)	1051.4 (68.2)	257.4 (87.1)	0.02 ^{**} ^	
Maximum Achieved HR (bpm)					
MCT Group	167.4 (8.4)	166.5 (8.2)	-1.0 (7.1)	0.71	0.20
IT Group	171.3 (11.5)	175.4 (9.8)	4.1 (7.7)	0.21	
Maximum O ₂ pulse (ml/beat)					
MCT Group	12.2 (2.9)	12.2 (2.4)	.02 (1.1)	0.95	0.47
IT Group	12.6 (2.0)	13.4 (2.0)	.90 (3.3)	0.51	
Treadmill Duration (seconds) (at 85% predicted max HR)					
MCT Group	347 (219)	422 (250)	74 (77)	0.02 ^{**}	0.03 ^{**}
IT Group	371 (123)	595 (141)	224 (163)	0.01 ^{**}	

^ Non-parametric analyses. Wilcoxon test for within-group and Mann-Whitney U test for between-group comparison. Significant difference: **p* = 0.05; ***p* < 0.05.

Table 3.4 Body Composition Pre- and Post-Intervention [Mean (SD)]

Variable	Pre MCT (n = 10) IT (n = 7)	Post MCT (n = 9) IT (n = 7)	Change	P for within group change	P for between group change
Weight (pounds)					
MCT Group	196.7 (39.9)	182.3 (38.9)	- 14.4 (9.0)	0.005** ^	
IT Group	183.9 (15.3)	171.8 (19.6)	-12.1 (7.0)	0.004**	0.74 ^
BMI (kg m ⁻²)					
MCT Group	33.3 (6.0)	30.9 (5.8)	- 2.5 (1.6)	0.005** ^	
IT Group	31.1 (4.4)	28.9 (4.6)	- 2.2 (1.4)	0.006**	0.96 ^
Fat mass (%)					
MCT Group	48.6 (6.5)	44.6 (9.0)	- 4.0 (4.6)	0.02*	
IT Group	45.7 (5.9)	41.9 (8.0)	- 3.7 (3.6)	0.02* ^	0.81 ^
Absolute fat mass (kg)					
MCT Group	42.5 (13.2)	36.2 (13.1)	6.3 (4.4)	0.001**	
IT Group	36.5 (6.8)	31.6 (8.1)	4.8 (2.8)	0.004**	0.45
Absolute lean mass (kg)					
MCT Group	43.8 (7.7)	43.1 (6.9)	- .069 (2.5)	0.41	
IT Group	43.0 (4.3)	43.0 (4.9)	.003 (2.0)	0.99	0.56

^Non-parametric analyses. Wilcoxon test for within-group and Mann-Whitney U test for between-group comparison. Significant difference: *p < 0.05; **p < 0.01.

Table 3.5 Participant Adherence to Exercise Intervention [Mean (SD)]

Variable	MCT (n = 10)	IT (n = 7)	P =
Cardiovascular exercise minutes (overall weekly average)	121.1 (29.5)	105.0 (24.1)	0.14
Resistance Training exercise (overall weekly average)	62.4 (14.0)	69.9 (12.6)	0.17
Cardiovascular exercise (Total Garmin minutes)	1200.1 (875.0)	1233.0 (879.0)	0.95
Average HR (Total Garmin minutes)	118.4 (8.9)	130.2 (8.9)	0.03*
Variables from self-reported weekly diet and exercise logs. Also, inclusion of cardiovascular exercise minutes and average HR were included from Garmin. Significant difference: *p < 0.05; **p < 0.01.			

Figure 3.1 Study Schema

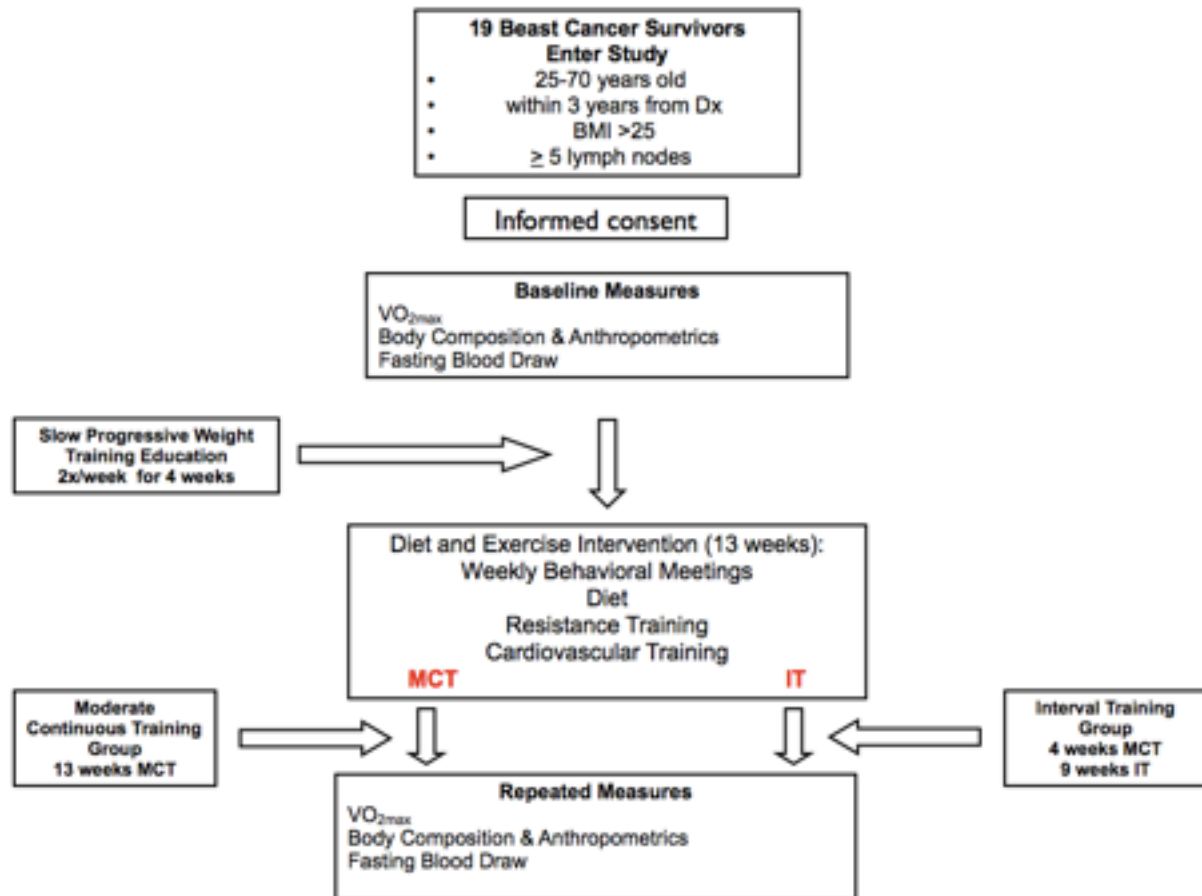


Figure 3.2 Flow of Participants Through Study

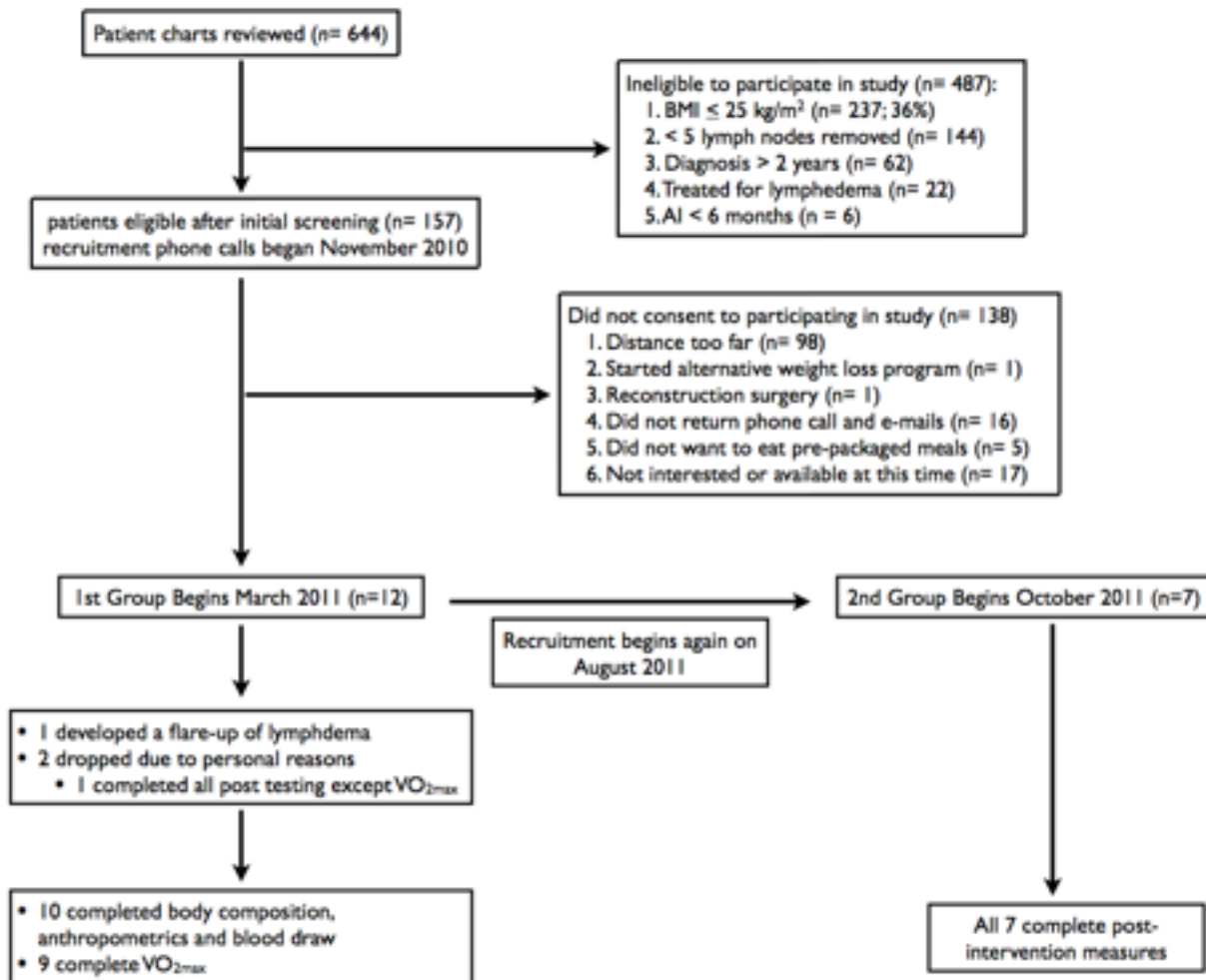


Figure 3.3 Individual Change in VO_{2max} ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).
Horizontal dotted line represents $28 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$.

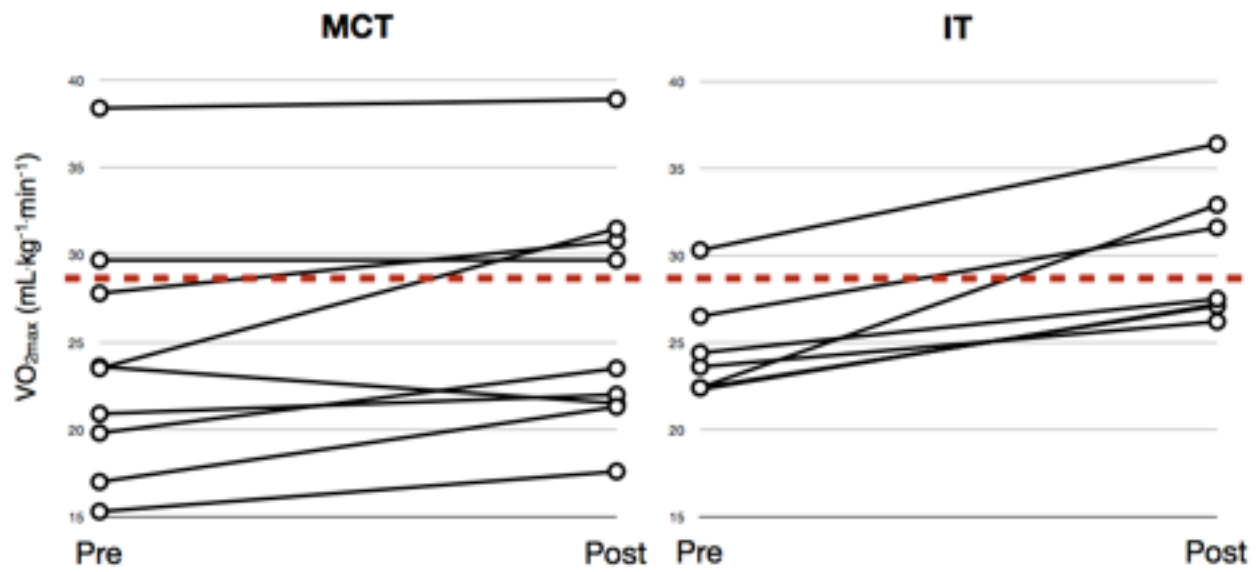


Figure 3.4 Association Between $VO_{2\max}$ and Cardiovascular Exercise Intensity (average HR) Retrieved from HR Monitor.

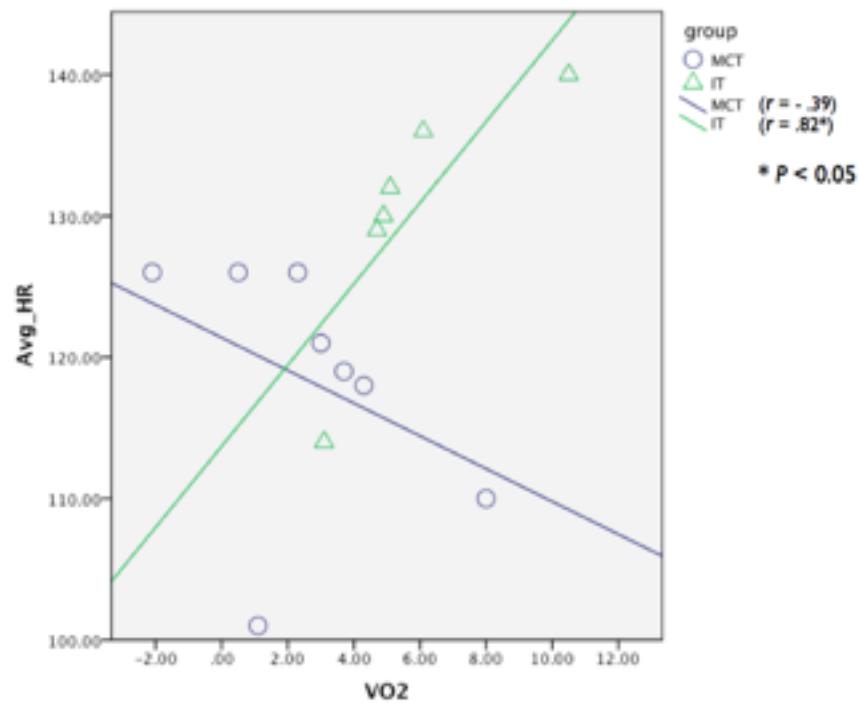
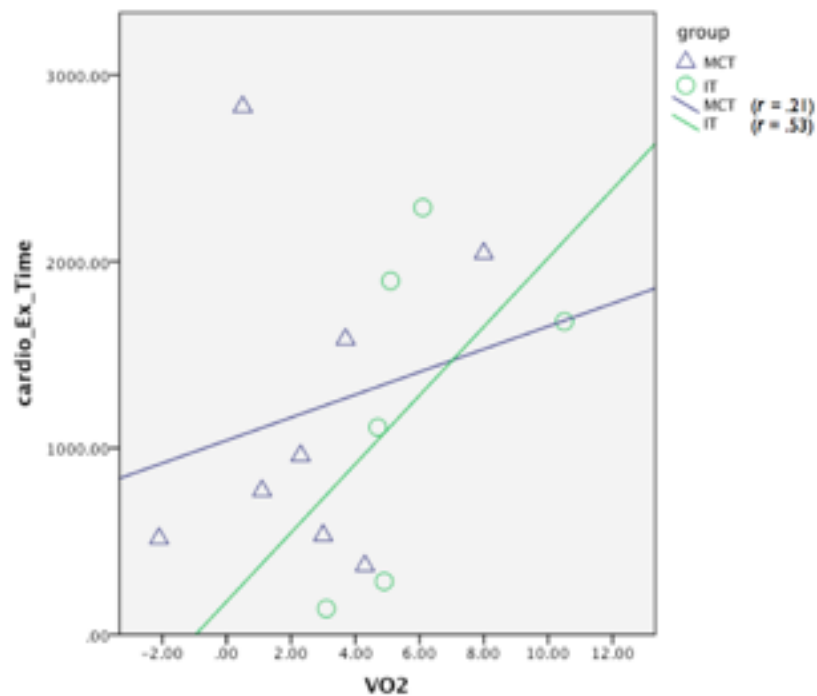


Figure 3.5 Association Between $VO_{2\max}$ and Cardiovascular Exercise Time Retrieved from HR Monitor.



Chapter 4

Conclusion

4.1 Summary

The overarching goal of this dissertation research was to add to the limited existing knowledge in the literature relevant to exercise interventions for breast cancer survivors. Initially, we determined that a majority of breast cancer survivors in our study have a low VO_{2max} compared to their age-matched healthy normal values. Also, we identified that submaximal treadmill testing may be used as a future objective measure for cardiorespiratory fitness, which could be used in a variety of clinical settings for breast cancer survivors. Moreover, our findings support a home-based combined diet and exercise intervention for improving weight and VO_{2max} in breast cancer survivors. Lastly, the results of our novel investigations suggest that IT elicited significantly greater improvements in VO_{2max} versus moderate exercise intensity.

Chapter 2

The work associated with Chapter 2 provides knowledge about cardiorespiratory fitness assessment for breast cancer survivors. An objective measure of cardiorespiratory fitness has been lacking in the field of breast cancer. We determined that 70% of the thirty breast cancer survivors we performed a maximal cardiorespiratory test on had a low cardiorespiratory fitness level. Low cardiorespiratory fitness in breast cancer survivors may be due to direct treatment effects, indirect effects of lifestyle change, or a combination of both. Much work is needed to determine the moderating effects different breast cancer treatment regimens have on cardiorespiratory fitness. Also, more studies will be useful for gathering data on subsequent change in activity levels and cardiorespiratory fitness pre- to post-treatment for breast cancer. More

knowledge about the factors associated with changes in cardiorespiratory fitness may help identify women who may benefit the most for exercise training to improve cardiorespiratory fitness.

A major reason why cardiorespiratory fitness has not been measured from an objective test is due to the cost of equipment and staff required to perform maximal cardiorespiratory testing. In response to this barrier, we showed that sub-maximal tests strongly correlate with the gold-standard maximal test for measuring cardiorespiratory fitness in breast cancer survivors. Furthermore, we determined that submaximal VO_2 at an endpoint based on HR had the strongest correlation. More work will be helpful in validating a submaximal VO_2 test to a maximal test. After a robust validation study is completed, we may be able to use a submaximal test that does not require gas analysis and uses the 85% APHRM endpoint, which can be used in breast cancer survivors.

Clinical implications from Chapter 2 suggest that breast cancer survivors may benefit from a cardiorespiratory fitness assessment. Additionally, the results from Chapter 2 showed that a submaximal treadmill test that used 85% APHRM had the strongest correlation of the two modalities and three submaximal endpoints. Therefore, a study adequately powered to validate a submaximal test using the 85% APMHR may be considered to provide an objective measure of fitness in breast cancer survivors.

Chapter 3

The findings from the research in Chapter 3 expand on the body of knowledge in exercise interventions for breast cancer survivors. Exercise interventions using combined diet and exercise appear to produce greater improvements in CVD and

breast cancer risk factors versus diet or exercise alone. Breast cancer survivors desire home-based interventions and this preference may improve sustainability for creating life-style behavior modification. However, there is a paucity of data to indicate that home-based interventions are feasible to produce meaningful improvement in targeted outcomes. In order to add to the gap in the literature concerning home-based interventions, we conducted this study to determine the feasibility of a combined diet and exercise intervention using a home-based design.

In addition, this study provides knowledge to an existing gap in the literature relating to exercise interventions for breast cancer survivors. Specifically, it's unknown if IT can provide a greater impact for improving weight loss or increased VO_{2max} compared to moderate exercise intensity, until the completion of this novel study. Our results suggest that participants prescribed IT can achieve significantly greater improvements in VO_{2max} versus MCT. Moreover, our study used IT in a home-based study without any adverse events directly related to the increased cardiovascular exercise dose. However, more studies are needed before conclusions can be made about the most effective exercise strategy for breast cancer survivors. The knowledge gained in this study can be used as exercise methodology in a multi-center randomized design aimed at improving an important CVD and breast cancer risk factor $\sim VO_{2max}$. Therefore, the collection of information relating to IT from this study and future work may eventually aid clinicians in their decision making concerning exercise prescriptions for breast cancer survivors.

4.2 Limitations

General Limitations of this Dissertation

Most, if not all, projects must overcome certain inherent limitations and obstacles during the lifetime of the study. This dissertation had unique challenges since it was integrated with a pre-established behavioral modification program led by a multidisciplinary team including a health behavioral psychologist and a registered dietitian. Although, the integration of the exercise dosing methodology into existing diet and exercise protocols produced unique challenges, the knowledge I gained from the dissertation was invaluable. Working side-by-side with a dietitian and health behavioral psychologist provided a rich educational experience. This learning environment allowed additional tools to be added to my existing clinical toolbox for the development of future treatment strategies. The following limitations, clinical implications, and future directions will include certain study characteristics related to combining my dissertation with an existing program.

Cardiorespiratory Fitness in Breast Cancer Survivors

Although we used the “gold standard” measure for cardiorespiratory fitness ($\text{VO}_{2\text{max}}$), we did not use a control group for comparison to our group of breast cancer survivors. A control group of women at high-risk for breast cancer with a similar CVD risk profile could have been a better comparison group to breast cancer survivors versus healthy female normative values for assessing cardiorespiratory fitness in Chapter 2. Also, additional analyses of cardiorespiratory fitness in women at high-risk

for breast cancer may detect a need for early intervention to improve fitness in this population.

Our study (Chapter 3) did not use a sedentary control group to evaluate the comparison of our Energy Balance Program to individuals not participating in a diet and exercise intervention. Because weight loss and improved cardiorespiratory fitness has shown to improve health outcomes for breast cancer survivors, we felt it was important to involve all participants in an intervention to improve their weight and cardiorespiratory fitness.

Association of Submaximal and Maximal Cardiorespiratory Tests

Although VO_2 at an endpoint based on HR had the strongest correlation in Chapter 2, more work should be performed to suggest a valid test for breast cancer survivors. A validation study will allow a more powerful conclusion for the use of a submaximal test as a surrogate to a maximal cardiorespiratory test.

Breast cancer survivors report observationally that they prefer stationary exercise equipment similar to an elliptical trainer. This preference initiated a desire by the our study team for assessing cardiorespiratory fitness on an Arc Trainer. However, we were limited in our ability to design a standardized exercise testing protocol while using an Arc Trainer as a modality to analyze submaximal VO_2 (Chapter 2). Although we manually adjusted the workload to allow a gradual and linear increase in HR and VO_2 , a standardized protocol was not used for all subjects. A study to assess physiological responses to an Arc Trainer will be helpful for determining an accurate testing protocol, if future work is performed using this equipment modality.

Small Sample Size

A larger sample of breast cancer survivors in Chapter 3 that could have been randomly assigned to a MCT or IT group would have provided a better generalization of the entire population of breast cancer survivors. It is reported that 62% of breast cancer survivors are overweight (Irwin, et al., 2005) and 36% are sedentary (Jones, et al., 2004), while the average age of a breast cancer survivor is 61 (Hayat, et al., 2007). Participants across both groups in Chapter 3 were generally inactive 12/17 (71%), all overweight/obese and the average age was 53. It is possible that only highly motivated breast cancer survivors agreed to participate in the intervention. Therefore, improvements in risk factors found in our study can only suggest that the entire population of breast cancer survivors can see the same positive changes in cardiorespiratory fitness and body composition measures.

Furthermore, women who were > 3 years from initial diagnosis of breast cancer were excluded from the home-based diet and exercise intervention in Chapter 3. There is evidence suggesting that cardiac function abnormalities may increase over time after being treated with cardiotoxic chemotherapy agents (Shan, et al., 1996). Thus, if a more heterogeneous group of breast cancer survivors that included women up to 10 years post-diagnosis are studied, it is possible they may have a more profound decline in cardiorespiratory fitness. In summary, we may want to consider demographics, treatment regimen, stage of tumor, lifestyle-related characteristics, and time since diagnosis in future randomized controlled trials with a robust sample size in order to study a group of women who are as representative as possible of the entire breast cancer survivor population.

Data Reporting During Home-Based Study

Even though it may be a challenge for breast cancer survivors to consistently participate in exercise routines away from home due to time and travel, supervised exercise programs provide a more easily controlled setting for participants. A highly supervised exercise setting may help assure that participants comply with the prescribed exercise time and intensity. However, for the positive effects of exercise training programs to remain sustainable, we should consider the preference of breast cancer survivors to perform exercise in their home environment versus visiting a facility away from home (Jones & Courneya, 2002; Rogers, et al., 2007; Rogers, et al., 2009). Therefore, this dissertation used a home-based model for an exercise intervention. More work is needed to determine if the gains in cardiorespiratory fitness are sustainable for two to five years after initiating home-based interventions.

We collected total time in minutes and HR during cardiovascular exercise. However, as previously mentioned, data downloaded from the HR monitors for the MCT and IT groups was 76% and 90% of total exercise time collected by self report. While a HR monitor will allow reliable exercise data, even the simplest devices can be a challenge for users. Nonetheless, exploring monitoring devices that can provide the greatest opportunity to collect the most data from study participants will be helpful for future trials.

We did not evaluate volume of cardiovascular exercise (time x intensity) to calculate metabolic equivalents (METs) for comparison between groups. We would have needed to capture the approximate speed of the various types of activities the participants performed in order to quantify an accurate estimation of METs per week of

exercise for both groups. However, we did identify that the MCT group performed more average minutes per week of cardiovascular exercise compared the IT group. On the other hand, the IT group reported a significantly higher average HR based on the total minutes collected from the HR monitor. Although we can not discern an estimated METs per week of exercise, we can suggest that the IT group, on average, exercised less per week with a higher corresponding HR.

Cardiorespiratory Fitness and Weight Training

All participants performed light resistance training as part of the existing Energy Balance Program. The addition of resistance training may have had a moderating effect on cardiorespiratory fitness. It has been reported that VO_{2max} significantly improved in a group of post-menopausal women performing high-intensity weight training alone (Brentano, et al., 2008). However, another study on heart failure patients reported a greater mean increase in VO_{2max} in an aerobic training group versus the aerobic plus resistance training group (Mandic, et al., 2009). Although, a resistance training protocol was used for the dissertation, the strength training was very light and the average weekly self-reported minutes was similar between groups. More work is needed to investigate the effect combined cardiovascular and resistance training has on targeted outcomes in breast cancer survivors including body composition and cardiorespiratory fitness. Studies that use cardiovascular training, weight training, or combined cardiovascular / weight training will add to our knowledge on cardiorespiratory and musculoskeletal fitness in breast cancer survivors.

Cardiorespiratory Fitness in Combined Versus Diet or Exercise Alone Interventions

The individual effect of diet and exercise alone must be considered when assessing the improvement of VO_{2max} after combined interventions. Specific to our study, we must use caution when associating improved VO_{2max} with an exercise intervention without considering the impact a calorie restricted diet may have on improvement in cardiorespiratory fitness. Is it possible to achieve significant improvement in VO_{2max} with weight loss alone or is exercise required to achieve this goal? Studies have been undertaken to address this question, but none include a cancer population. In a recent 12-week randomized intervention, obese participants were randomized to exercise only, calorie restriction only, or exercise and calorie restriction. The results indicated a significant increase in VO_{2max} from the exercise alone or the combined exercise and calorie restriction intervention (14% and 18%, respectively), but found no change in VO_{2max} in the calorie restriction alone group (Christiansen, et al., 2010). In a similar 6-month intervention in overweight (non-cancer) participants, caloric restriction only versus caloric restriction plus aerobic exercise versus weight maintenance diet, VO_{2max} significantly improved (increased) in the caloric restriction plus aerobic exercise arm only, 22+/-5% vs 7+/-5% (caloric restriction alone), vs -5+/-3% (weight maintenance diet) (Larson-Meyer, et al., 2010). Overall, interventions targeting cardiorespiratory fitness without exercise may not lead to significant improvements VO_{2max} .

4.3 Clinical Significance and Future Directions

The primary purpose of this dissertation research was to determine the effect of a home-based combined diet and exercise intervention (Energy Balance Program) on

VO_{2max} and weight loss in breast cancer survivors. In addition, we used an exercise training strategy for determining the effects of IT on VO_{2max} and weight loss in breast cancer survivors. The results demonstrated that an Energy Balance Program was feasible and could significantly improve VO_{2max} and body composition in breast cancer survivors. Furthermore, the results of this research demonstrated that participants prescribed IT had a significantly greater increase in VO_{2max} versus MCT.

This dissertation work can have clinical implications, since increasing cardiorespiratory fitness (measured as VO_{2max}) has been associated with a decrease in all-cause mortality and CVD in apparently healthy men and women. Each one metabolic equivalent [1 metabolic equivalent (MET) = 3.5 mL·kg⁻¹·min⁻¹] increase in VO_{2max} corresponded to an 11-13% and 15-18% reduction of all-cause mortality and CVD respectively (Barlow, et al., 2012; Kodama, et al., 2009). In our study, the IT group experienced a 5.3 mL·kg⁻¹·min⁻¹ improvement, while the MCT saw a significantly lower improvement in VO_{2max} at 2.3 mL·kg⁻¹·min⁻¹. Based on these previous results of Barlow et al. and Kodama et al., both groups were able to reduce their risk for all-cause mortality and CVD. Furthermore, our study led to significant improvements in cardiorespiratory fitness for breast cancer survivors who are high-risk for all-cause mortality and CVD compared to their non-cancer age matched peers.

This dissertation research has laid the groundwork for novel diet and exercise interventions for breast cancer survivors. A future goal of this research is to better understand the most effective cardiovascular exercise dose to elicit the greatest improvement in cardiorespiratory fitness and body composition in breast cancer survivors. Additionally, we would like to determine how to create sustainability into

cancer survivors life-style behavior so the positive effects of interventions impact long-term health outcomes. Therefore, the collective integration of the current literature and the results from this dissertation provide direction for future research.

Integration of a Novel Exercise Prescription Into an Existing Program

Exercise training has been suggested by clinicians for several years due to the benefits to cellular and functional systems. However, as clinicians, we are challenged with changing human behavior for successfully implementing long-term lifestyle change. Even though this dissertation work faced some challenges, the experience has led to a better all-around clinical view on cancer survivorship care, especially when considering the health behavior aspect of life-style modification. Observationally, women reported it would be difficult to find the time for travel to supervised exercise sessions on a regular basis. Also, the breast cancer survivors in our study commented they would be less comfortable exercising around people in a fitness facility. Therefore, we should consider future studies that focus on participant preferences for the environment that allows the best chance for sustainable improvements in health outcomes.

Exercise variety may influence the compliance of long-term behavior modification for breast cancer survivors. It's been shown that children prefer shorter bouts of high-intensity exercise that resembles play compared to longer distance moderate exercise (Barkley, Epstein, & Roemmich, 2009). As adults, are we not similar to children when it comes to boredom with exercise? Women in the IT group also commented that their prescribed HR range provided a motivational tool which kept them engaged in the cardiovascular exercise. Lastly, participants in both the MCT and IT groups voiced their

concern about the resistance training protocol. Specifically, the resistance training protocol was too long and the participants lost interest in completing the prescribed resistance exercises. As a result of the observations noted, we should consider future interventions that include exercise regimens that have a chance to maintain motivation in order to achieve long-term behavior modification. A creative mix of resistance and endurance exercises may provide an ongoing cardiovascular workout that may aid in motivation and have a moderating effect on improved lean mass and cardiorespiratory fitness.

Home-based Diet and Exercise Interventions

As previously stated in Chapter 3, some evidence points to a significant survival advantage for breast cancer survivors who engage in combined diet and exercise behavioral change versus exercise or diet alone (Pierce, et al., 2007). Many interventions for breast cancer survivors can be delivered in a highly supervised environment and require patients to attend 2-3 sessions per week. However, the cost of monitored and supervised interventions and the demands on time and travel for cancer survivors may be significant barriers to the implementation of these interventions (Pekmezi & Demark-Wahnefried, 2011). Therefore, Pekmezi et al. indicated there is a need to investigate home-based lifestyle interventions for cancer survivors as they may be more sustainable and applicable to the growing cancer survivor population (Pekmezi & Demark-Wahnefried, 2011). As a result it seems like a natural progression from highly supervised interventions to home-based programs that may favor sustainable life-style behavior modification. Lastly, disseminating interventions to a large number of breast

cancer survivors is important in order to have a meaningful impact. In response to these issues concerning sustainability and dissemination, we are currently preparing a proposal, based on this dissertation data, for a National Cancer Institute supported study. We plan to lead a multi-center RCT using a home-based combined diet and exercise intervention targeting VO_{2max} and other secondary risk factors in breast cancer survivors.

Interval Training

Emerging evidence suggests that poor cardiorespiratory fitness may play an important role in the the late adverse effects after breast cancer treatment including cardiac dysfunction and a worse CVD risk profile (Jones, Haykowsky, Peddle, et al., 2007; Jones, Haykowsky, Pituskin, et al., 2007). Despite the impact cardiorespiratory fitness may have on breast cancer outcomes after diagnosis, survivors still have a low cardiorespiratory fitness level. Our work (Chapters 2 and 3) demonstrated the majority of breast cancer survivors have a significantly lower VO_{2max} compared to age-matched normative values. Additionally, a recent study indicated that breast cancer survivors have a significantly lower VO_{2max} compared to age-matched healthy controls (Jones, Haykowsky, Pituskin, et al., 2007). The reason for a low cardiorespiratory fitness level remains unclear, but cardiotoxic treatment agents and inactivity are thought to collectively contribute to an impairment in oxygen delivery and utilization (Jones, Haykowsky, Swartz, et al., 2007).

Previous studies have demonstrated that physical activity interventions have been successful at improving cardiorespiratory fitness in breast cancer survivors

(McNeely, et al., 2006; K. H. Schmitz, Holtzman, et al., 2005), However, additional exercise trials are needed to explore the effects of different exercise prescriptions and dosing intensity in breast cancer survivors (Neilson, et al., 2009). Cardiovascular exercise dosing intensity has been used in other populations. For example, IT at higher intensities has shown to be superior to continuous training at moderate levels for improving VO_{2max} with sedentary (Daussin, et al., 2008), chronic obstructive pulmonary disease (Butcher & Jones, 2006), CAD (Cornish, et al., 2010), and athletic (McArdle, 2007) populations. Therefore, it seems logical to investigate the effects of IT during a home-based combined diet and exercise intervention for breast cancer survivors. Additionally, a better understanding of the ability to disseminate IT methodology to a larger number of breast cancer survivors will contribute to the field of breast cancer survivorship.

4.4 Conclusion

The collection of research conducted and presented in this dissertation has established new information that may impact health outcomes for breast cancer survivors. A novel cardiovascular exercise training strategy was incorporated into a home-based intervention that may be disseminated to a large number of breast cancer survivors. Clinicians may consider the home-based environment conducive to providing an intervention that successfully improves targeted outcomes for breast cancer survivors. Also, the IT group revealed significantly greater improvements in a well known CVD and breast cancer risk factor (VO_{2max}) compared to the MCT group. Therefore, clinicians may consider using IT when designing exercise programs for

breast cancer survivors. This dissertation has helped add to the field of knowledge related to breast cancer survivorship care. However, additional research will build upon our current work and may aid in improving the overall quality of life in breast cancer survivors; and possibly other populations of cancer survivors.

Bibliography

- ACS. (2011). Cancer Facts and Figures 2011. Retrieved November 3rd, 2011, from <http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2011>
- ACS. (2012). Cancer Facts and Figures 2012. Retrieved May 11, 2012, from <http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2011>
- ACSM. (2006). *ACSM's guidelines for exercise testing and prescription* (7th ed.). Baltimore: Lippincott, Williams & Wilkins.
- ACSM. (2009). *ACSM's guidelines for exercise testing and prescription* (8th ed.). Baltimore: Lippincott, Williams & Wilkins.
- Aleman, B. M., van den Belt-Dusebout, A. W., De Bruin, M. L., van 't Veer, M. B., Baaijens, M. H., de Boer, J. P., et al. (2007). Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood*, 109(5), 1878-1886.
- Andrykowski, M. A., Curran, S. L., & Lightner, R. (1998). Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med*, 21(1), 1-18.
- Arnardottir, R. H., Boman, G., Larsson, K., Hedenstrom, H., & Emtner, M. (2007). Interval training compared with continuous training in patients with COPD. *Respir Med*, 101(6), 1196-1204.
- ASCO. (2007). ASCO Clinical Evidence Review on the Ongoing Care of Adult Cancer Survivors: Cardiac and Pulmonary Late Effects- Review Summary. *Journal of Oncology Practice*, 3(4), 233-235.

- Baer, H. J., Colditz, G. A., Rosner, B., Michels, K. B., Rich-Edwards, J. W., Hunter, D. J., et al. (2005). Body fatness during childhood and adolescence and incidence of breast cancer in premenopausal women: a prospective cohort study. *Breast Cancer Res*, 7(3), R314-325.
- Balke B, W. R. (1959). An experimental study of physical fitness in Air Force personnel. *US Armed Forces Med J*, 10, 675-688.
- Baquet, G., Gamelin, F. X., Mucci, P., Thevenet, D., Van Praagh, E., & Berthoin, S. (2010). Continuous vs. interval aerobic training in 8- to 11-year-old children. *J Strength Cond Res*, 24(5), 1381-1388.
- Bardia, A., Arieas, E. T., Zhang, Z., Defilippis, A., Tarpinian, K., Jeter, S., et al. (2012). Comparison of breast cancer recurrence risk and cardiovascular disease incidence risk among postmenopausal women with breast cancer. *Breast Cancer Res Treat*, 131(3), 907-914.
- Barkley, J. E., Epstein, L. H., & Roemmich, J. N. (2009). Reinforcing value of interval and continuous physical activity in children. *Physiol Behav*, 98(1-2), 31-36.
- Barlow, C. E., Defina, L. F., Radford, N. B., Berry, J. D., Cooper, K. H., Haskell, W. L., et al. (2012). Cardiorespiratory fitness and long-term survival in "low-risk" adults. *J Am Heart Assoc*, 1(4), e001354.
- Bear, H. D., Anderson, S., Smith, R. E., Geyer, C. E., Jr., Mamounas, E. P., Fisher, B., et al. (2006). Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*, 24(13), 2019-2027.

- Befort, C. A., Klemp, J. R., Austin, H. L., Perri, M. G., Schmitz, K. H., Sullivan, D. K., et al. (2012). Outcomes of a weight loss intervention among rural breast cancer survivors. *Breast Cancer Res Treat*, 132(2), 631-639.
- Bernardi, M., Guerra, E., Di Giacinto, B., Di Cesare, A., Castellano, V., & Bhambhani, Y. (2010). Field evaluation of paralympic athletes in selected sports: implications for training. *Med Sci Sports Exerc*, 42(6), 1200-1208.
- Bird, B. R., & Swain, S. M. (2008). Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res*, 14(1), 14-24.
- Blair, S. N., & Church, T. S. (2004). The fitness, obesity, and health equation: is physical activity the common denominator? *JAMA*, 292(10), 1232-1234.
- Blair, S. N., Kampert, J. B., Kohl, H. W., 3rd, Barlow, C. E., Macera, C. A., Paffenbarger, R. S., Jr., et al. (1996). Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*, 276(3), 205-210.
- Blair, S. N., Kohl, H. W., 3rd, Barlow, C. E., Paffenbarger, R. S., Jr., Gibbons, L. W., & Macera, C. A. (1995). Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA*, 273(14), 1093-1098.
- Blair, S. N., Kohl, H. W., 3rd, Paffenbarger, R. S., Jr., Clark, D. G., Cooper, K. H., & Gibbons, L. W. (1989). Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*, 262(17), 2395-2401.
- Blair, S. N., LaMonte, M. J., & Nichaman, M. Z. (2004). The evolution of physical activity recommendations: how much is enough? *Am J Clin Nutr*, 79(5), 913S-920S.

- Bonnetterre, J., Roche, H., Kerbrat, P., Fumoleau, P., Goudier, M. J., Fargeot, P., et al. (2004). Long-term cardiac follow-up in relapse-free patients after six courses of fluorouracil, epirubicin, and cyclophosphamide, with either 50 or 100 mg of epirubicin, as adjuvant therapy for node-positive breast cancer: French adjuvant study group. *J Clin Oncol*, 22(15), 3070-3079.
- Brentano, M. A., Cadore, E. L., Da Silva, E. M., Ambrosini, A. B., Coertjens, M., Petkowicz, R., et al. (2008). Physiological adaptations to strength and circuit training in postmenopausal women with bone loss. *J Strength Cond Res*, 22(6), 1816-1825.
- Butcher, S. J., & Jones, R. L. (2006). The impact of exercise training intensity on change in physiological function in patients with chronic obstructive pulmonary disease. *Sports Med*, 36(4), 307-325.
- Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*, 348(17), 1625-1638.
- Cardinale, D., Sandri, M. T., Colombo, A., Colombo, N., Boeri, M., Lamantia, G., et al. (2004). Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*, 109(22), 2749-2754.
- Carlson, L. E., Smith, D., Russell, J., Fibich, C., & Whittaker, T. (2006). Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study. *Bone Marrow Transplant*, 37(10), 945-954.
- Casaburi, R. (1994). Physiologic responses to training. *Clin Chest Med*, 15(2), 215-227.

- Casaburi, R., Patessio, A., Ioli, F., Zanaboni, S., Donner, C. F., & Wasserman, K. (1991). Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis*, 143(1), 9-18.
- Christiansen, T., Paulsen, S. K., Bruun, J. M., Pedersen, S. B., & Richelsen, B. (2010). Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study. *Am J Physiol Endocrinol Metab*, 298(4), E824-831.
- Civelli, M., Cardinale, D., Martinoni, A., Lamantia, G., Colombo, N., Colombo, A., et al. (2006). Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiac toxicity. *Int J Cardiol*, 111(1), 120-126.
- Clarke, C. A., Purdie, D. M., & Glaser, S. L. (2006). Population attributable risk of breast cancer in white women associated with immediately modifiable risk factors. *BMC Cancer*, 6, 170.
- Clements, I. P., Davis, B. J., & Wiseman, G. A. (2002). Systolic and diastolic cardiac dysfunction early after the initiation of doxorubicin therapy: significance of gender and concurrent mediastinal radiation. *Nucl Med Commun*, 23(6), 521-527.
- Cornish, A. K., Broadbent, S., & Cheema, B. S. (2010). Interval training for patients with coronary artery disease: a systematic review. *Eur J Appl Physiol*.
- Courneya, K. S., & Friedenreich, C. M. (2001). Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med*, 23(4), 263-272.

- Cuppone, F., Bria, E., Verma, S., Pritchard, K. I., Gandhi, S., Carlini, P., et al. (2008). Do adjuvant aromatase inhibitors increase the cardiovascular risk in postmenopausal women with early breast cancer? Meta-analysis of randomized trials. *Cancer*, 112(2), 260-267.
- Daussin, F. N., Ponsot, E., Dufour, S. P., Lonsdorfer-Wolf, E., Doutreleau, S., Geny, B., et al. (2007). Improvement of VO₂max by cardiac output and oxygen extraction adaptation during intermittent versus continuous endurance training. *Eur J Appl Physiol*, 101(3), 377-383.
- Daussin, F. N., Zoll, J., Dufour, S. P., Ponsot, E., Lonsdorfer-Wolf, E., Doutreleau, S., et al. (2008). Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects. *Am J Physiol Regul Integr Comp Physiol*, 295(1), R264-272.
- Demark-Wahnefried, W., & Jones, L. W. (2008). Promoting a healthy lifestyle among cancer survivors. *Hematol Oncol Clin North Am*, 22(2), 319-342, viii.
- Demark-Wahnefried, W., Peterson, B. L., Winer, E. P., Marks, L., Aziz, N., Marcom, P. K., et al. (2001). Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol*, 19(9), 2381-2389.
- Dimopoulos, S., Anastasiou-Nana, M., Sakellariou, D., Drakos, S., Kapsimalakou, S., Maroulidis, G., et al. (2006). Effects of exercise rehabilitation program on heart rate recovery in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil*, 13(1), 67-73.

- Donohoe, C. L., Doyle, S. L., & Reynolds, J. V. (2011). Visceral adiposity, insulin resistance and cancer risk. *Diabetol Metab Syndr*, 3, 12.
- Doyle, C., Kushi, L. H., Byers, T., Courneya, K. S., Demark-Wahnefried, W., Grant, B., et al. (2006). Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin*, 56(6), 323-353.
- Duncan, G. E., Anton, S. D., Sydemann, S. J., Newton, R. L., Jr., Corsica, J. A., Durning, P. E., et al. (2005). Prescribing exercise at varied levels of intensity and frequency: a randomized trial. *Arch Intern Med*, 165(20), 2362-2369.
- Eheman, C., Henley, S. J., Ballard-Barbash, R., Jacobs, E. J., Schymura, M. J., Noone, A. M., et al. (2012). Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer*, 118(9), 2338-2366.
- Eloranta, S., Lambert, P. C., Andersson, T. M., Czene, K., Hall, P., Bjorkholm, M., et al. (2012). Partitioning of excess mortality in population-based cancer patient survival studies using flexible parametric survival models. *BMC Med Res Methodol*, 12(1), 86.
- Eng, J. J., Dawson, A. S., & Chu, K. S. (2004). Submaximal exercise in persons with stroke: test-retest reliability and concurrent validity with maximal oxygen consumption. *Arch Phys Med Rehabil*, 85(1), 113-118.
- Ewer, M. S., Swain, S. M., Cardinale, D., Fadol, A., & Suter, T. M. (2011). Cardiac dysfunction after cancer treatment. *Tex Heart Inst J*, 38(3), 248-252.

- Ferguson, S., Gledhill, N., Jamnik, V. K., Wiebe, C., & Payne, N. (2001). Cardiac performance in endurance-trained and moderately active young women. *Med Sci Sports Exerc*, 33(7), 1114-1119.
- Friedenreich, C. M., Neilson, H. K., Woolcott, C. G., McTiernan, A., Wang, Q., Ballard-Barbash, R., et al. (2011). Changes in insulin resistance indicators, insulin-like growth factors, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. *Endocr Relat Cancer*.
- Gallagher, E. J., & LeRoith, D. (2011). Minireview: IGF, Insulin, and Cancer. *Endocrinology*, 152(7), 2546-2551.
- Galvao, D. A., & Newton, R. U. (2005). Review of exercise intervention studies in cancer patients. *J Clin Oncol*, 23(4), 899-909.
- Gitt, A. K., Wasserman, K., Kilkowski, C., Kleemann, T., Kilkowski, A., Bangert, M., et al. (2002). Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation*, 106(24), 3079-3084.
- Gledhill, N., Cox, D., & Jamnik, R. (1994). Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc*, 26(9), 1116-1121.
- Goodwin, P. J. (2008). Insulin in the adjuvant breast cancer setting: a novel therapeutic target for lifestyle and pharmacologic interventions? *J Clin Oncol*, 26(6), 833-834.
- Goodwin, P. J., Ennis, M., Pritchard, K. I., Trudeau, M. E., Koo, J., Madarnas, Y., et al. (2002). Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*, 20(1), 42-51.

- Gottdiener, J. S., Mathisen, D. J., Borer, J. S., Bonow, R. O., Myers, C. E., Barr, L. H., et al. (1981). Doxorubicin cardiotoxicity: assessment of late left ventricular dysfunction by radionuclide cineangiography. *Ann Intern Med*, 94(4 pt 1), 430-435.
- Harvey, P. J., Picton, P. E., Su, W. S., Morris, B. L., Notarius, C. F., & Floras, J. S. (2005). Exercise as an alternative to oral estrogen for amelioration of endothelial dysfunction in postmenopausal women. *Am Heart J*, 149(2), 291-297.
- Hayat, M. J., Howlader, N., Reichman, M. E., & Edwards, B. K. (2007). Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist*, 12(1), 20-37.
- Hewitt, M., Rowland, J. H., & Yancik, R. (2003). Cancer survivors in the United States: age, health, and disability. *J Gerontol A Biol Sci Med Sci*, 58(1), 82-91.
- Holmes, M. D., Chen, W. Y., Feskanich, D., Kroenke, C. H., & Colditz, G. A. (2005). Physical activity and survival after breast cancer diagnosis. *JAMA*, 293(20), 2479-2486.
- Howell, A., Cuzick, J., Baum, M., Buzdar, A., Dowsett, M., Forbes, J. F., et al. (2005). Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*, 365(9453), 60-62.
- Huisamen, B., Dietrich, D., Bezuidenhout, N., Lopes, J., Flepisi, B., Blackhurst, D., et al. (2012). Early cardiovascular changes occurring in diet-induced, obese insulin-resistant rats. *Mol Cell Biochem*.

- Irwin, M. L., Alvarez-Reeves, M., Cadmus, L., Mierzejewski, E., Mayne, S. T., Yu, H., et al. (2009). Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. *Obesity (Silver Spring)*, 17(8), 1534-1541.
- Irwin, M. L., Crumley, D., McTiernan, A., Bernstein, L., Baumgartner, R., Gilliland, F. D., et al. (2003). Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer*, 97(7), 1746-1757.
- Irwin, M. L., McTiernan, A., Baumgartner, R. N., Baumgartner, K. B., Bernstein, L., Gilliland, F. D., et al. (2005). Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. *J Clin Oncol*, 23(4), 774-782.
- Janni, W., & Hepp, P. (2010). Adjuvant aromatase inhibitor therapy: outcomes and safety. *Cancer Treat Rev*, 36(3), 249-261.
- Jolliffe, J. A., Rees, K., Taylor, R. S., Thompson, D., Oldridge, N., & Ebrahim, S. (2000). Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*(4), CD001800.
- Jones, L. W., & Courneya, K. S. (2002). Exercise counseling and programming preferences of cancer survivors. *Cancer Pract*, 10(4), 208-215.
- Jones, L. W., Courneya, K. S., Fairey, A. S., & Mackey, J. R. (2004). Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: a single-blind, randomized controlled trial. *Ann Behav Med*, 28(2), 105-113.

- Jones, L. W., Douglas, P. S., Eves, N. D., Marcom, P. K., Kraus, W. E., Herndon, J. E., 2nd, et al. (2010). Rationale and design of the Exercise Intensity Trial (EXCITE): A randomized trial comparing the effects of moderate versus moderate to high-intensity aerobic training in women with operable breast cancer. *BMC Cancer*, 10, 531.
- Jones, L. W., Eves, N. D., Haykowsky, M., Freedland, S. J., & Mackey, J. R. (2009). Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. *Lancet Oncol*, 10(6), 598-605.
- Jones, L. W., Haykowsky, M., Peddle, C. J., Joy, A. A., Pituskin, E. N., Tkachuk, L. M., et al. (2007). Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab. *Cancer Epidemiol Biomarkers Prev*, 16(5), 1026-1031.
- Jones, L. W., Haykowsky, M., Pituskin, E. N., Jendzjowsky, N. G., Tomczak, C. R., Haennel, R. G., et al. (2007). Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor--positive operable breast cancer. *Oncologist*, 12(10), 1156-1164.
- Jones, L. W., Haykowsky, M. J., Swartz, J. J., Douglas, P. S., & Mackey, J. R. (2007). Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol*, 50(15), 1435-1441.
- Kemps, H. M., Schep, G., de Vries, W. R., Schmikli, S. L., Zonderland, M. L., Thijssen, E. J., et al. (2008). Predicting effects of exercise training in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*, 102(8), 1073-1078.

- King, A. C., Haskell, W. L., Taylor, C. B., Kraemer, H. C., & DeBusk, R. F. (1991). Group- vs home-based exercise training in healthy older men and women. A community-based clinical trial. *JAMA*, 266(11), 1535-1542.
- Klemp JR, C. S., Papsek S, Befort C, Khan QJ, Sharma P, Yeh HW, Fabian CJ. (2009). Feasibility of a Diet, Exercise and Behavior Modification Intervention for Post-Menopausal Breast Cancer Survivors. *Cancer Research*, 69(24), 557S.
- Klewer, S. E., Goldberg, S. J., Donnerstein, R. L., Berg, R. A., & Hutter, J. J., Jr. (1992). Dobutamine stress echocardiography: a sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. *J Am Coll Cardiol*, 19(2), 394-401.
- Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., et al. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*, 301(19), 2024-2035.
- Larson-Meyer, D. E., Redman, L., Heilbronn, L. K., Martin, C. K., & Ravussin, E. (2010). Caloric restriction with or without exercise: the fitness versus fatness debate. *Med Sci Sports Exerc*, 42(1), 152-159.
- Lind, P. A., Rosfors, S., Wennberg, B., Glas, U., Bevegard, S., & Fornander, T. (1998). Pulmonary function following adjuvant chemotherapy and radiotherapy for breast cancer and the issue of three-dimensional treatment planning. *Radiother Oncol*, 49(3), 245-254.

- Lloyd-Jones, D. M., Leip, E. P., Larson, M. G., D'Agostino, R. B., Beiser, A., Wilson, P. W., et al. (2006). Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*, 113(6), 791-798.
- Lu, T. W., Chien, H. L., & Chen, H. L. (2007). Joint loading in the lower extremities during elliptical exercise. *Med Sci Sports Exerc*, 39(9), 1651-1658.
- Lynch, B. M., Neilson, H. K., & Friedenreich, C. M. (2011). Physical activity and breast cancer prevention. *Recent Results Cancer Res*, 186, 13-42.
- Mandic, S., Tymchak, W., Kim, D., Daub, B., Quinney, H. A., Taylor, D., et al. (2009). Effects of aerobic or aerobic and resistance training on cardiorespiratory and skeletal muscle function in heart failure: a randomized controlled pilot trial. *Clin Rehabil*, 23(3), 207-216.
- Martin, M., Pienkowski, T., Mackey, J., Pawlicki, M., Guastalla, J. P., Weaver, C., et al. (2005). Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med*, 352(22), 2302-2313.
- McArdle, W., Katch, F., Katch, L. . (2007). *Exercise Physiology: Energy, Nutrition, & Human Performance*. (Sixth ed.). Philadelphia: Lippincott Williams & Wilkins.
- McNeely, M. L., Campbell, K. L., Rowe, B. H., Klassen, T. P., Mackey, J. R., & Courneya, K. S. (2006). Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ*, 175(1), 34-41.
- McTiernan, A., Irwin, M., & Vongruenigen, V. (2010). Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. *J Clin Oncol*, 28(26), 4074-4080.

- Mefferd, K., Nichols, J. F., Pakiz, B., & Rock, C. L. (2007). A cognitive behavioral therapy intervention to promote weight loss improves body composition and blood lipid profiles among overweight breast cancer survivors. *Breast Cancer Res Treat*, 104(2), 145-152.
- Michael, Y. L., Kawachi, I., Berkman, L. F., Holmes, M. D., & Colditz, G. A. (2000). The persistent impact of breast carcinoma on functional health status: prospective evidence from the Nurses' Health Study. *Cancer*, 89(11), 2176-2186.
- Moholdt, T. T., Amundsen, B. H., Rustad, L. A., Wahba, A., Lovo, K. T., Gullikstad, L. R., et al. (2009). Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J*, 158(6), 1031-1037.
- Munro, B. (1993). *Correlations*. Philadelphia: JP Lippincott.
- Muti, P., Quattrin, T., Grant, B. J., Krogh, V., Micheli, A., Schunemann, H. J., et al. (2002). Fasting glucose is a risk factor for breast cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev*, 11(11), 1361-1368.
- Nabholtz, J. M. (2008). Aromatase inhibitors in the management of early breast cancer. *Eur J Surg Oncol*, 34(11), 1199-1207.
- NCEP. (2002). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*, 106(25), 3143-3421.
- NCI. (SEER 1996-2007). from <http://seer.cancer.gov/statfacts/html/breast.html>

- Nechwatal, R. M., Duck, C., & Gruber, G. (2002). [Physical training as interval or continuous training in chronic heart failure for improving functional capacity, hemodynamics and quality of life--a controlled study]. *Z Kardiol*, 91(4), 328-337.
- Neilson, H. K., Friedenreich, C. M., Brockton, N. T., & Millikan, R. C. (2009). Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. *Cancer Epidemiol Biomarkers Prev*, 18(1), 11-27.
- Ng, R., Better, N., & Green, M. D. (2006). Anticancer agents and cardiotoxicity. *Semin Oncol*, 33(1), 2-14.
- Nichols, H. B., Trentham-Dietz, A., Egan, K. M., Titus-Ernstoff, L., Holmes, M. D., Bersch, A. J., et al. (2009). Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev*, 18(5), 1403-1409.
- Ooi, G. C., Kwong, D. L., Ho, J. C., Lock, D. T., Chan, F. L., Lam, W. K., et al. (2001). Pulmonary sequelae of treatment for breast cancer: a prospective study. *Int J Radiat Oncol Biol Phys*, 50(2), 411-419.
- Patnaik, J. L., Byers, T., DiGuseppi, C., Dabelea, D., & Denberg, T. D. (2011). Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res*, 13(3), R64.
- Patterson, R. E., Cadmus, L. A., Emond, J. A., & Pierce, J. P. (2010). Physical activity, diet, adiposity and female breast cancer prognosis: a review of the epidemiologic literature. *Maturitas*, 66(1), 5-15.

- Pedersen, B. K. (2009). The diseasome of physical inactivity--and the role of myokines in muscle--fat cross talk. *J Physiol*, 587(Pt 23), 5559-5568.
- Peel, J. B., Sui, X., Adams, S. A., Hebert, J. R., Hardin, J. W., & Blair, S. N. (2009). A prospective study of cardiorespiratory fitness and breast cancer mortality. *Med Sci Sports Exerc*, 41(4), 742-748.
- Pekmezi, D. W., & Demark-Wahnefried, W. (2011). Updated evidence in support of diet and exercise interventions in cancer survivors. *Acta Oncol*, 50(2), 167-178.
- Perez, E. A., Suman, V. J., Davidson, N. E., Kaufman, P. A., Martino, S., Dakhil, S. R., et al. (2004). Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. *J Clin Oncol*, 22(18), 3700-3704.
- Perri, M. G., Martin, A. D., Leermakers, E. A., Sears, S. F., & Notelovitz, M. (1997). Effects of group- versus home-based exercise in the treatment of obesity. *J Consult Clin Psychol*, 65(2), 278-285.
- Pierce, J. P., Stefanick, M. L., Flatt, S. W., Natarajan, L., Sternfeld, B., Madlensky, L., et al. (2007). Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. *J Clin Oncol*, 25(17), 2345-2351.
- Pinto, B. M., Maruyama, N. C., Clark, M. M., Cruess, D. G., Park, E., & Roberts, M. (2002). Motivation to modify lifestyle risk behaviors in women treated for breast cancer. *Mayo Clin Proc*, 77(2), 122-129.
- Poole, D. C., & Gaesser, G. A. (1985). Response of ventilatory and lactate thresholds to continuous and interval training. *J Appl Physiol*, 58(4), 1115-1121.

- Protani, M., Coory, M., & Martin, J. H. (2010). Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*, 123(3), 627-635.
- Renahan, A. G., Roberts, D. L., & Dive, C. (2008). Obesity and cancer: pathophysiological and biological mechanisms. *Arch Physiol Biochem*, 114(1), 71-83.
- Renahan, A. G., Tyson, M., Egger, M., Heller, R. F., & Zwahlen, M. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*, 371(9612), 569-578.
- Rogers, L. Q., Courneya, K. S., Shah, P., Dunnington, G., & Hopkins-Price, P. (2007). Exercise stage of change, barriers, expectations, values and preferences among breast cancer patients during treatment: a pilot study. *Eur J Cancer Care (Engl)*, 16(1), 55-66.
- Rogers, L. Q., Courneya, K. S., Verhulst, S., Markwell, S. J., & McAuley, E. (2008). Factors associated with exercise counseling and program preferences among breast cancer survivors. *J Phys Act Health*, 5(5), 688-705.
- Rogers, L. Q., Markwell, S. J., Verhulst, S., McAuley, E., & Courneya, K. S. (2009). Rural breast cancer survivors: exercise preferences and their determinants. *Psychooncology*, 18(4), 412-421.
- Rognmo, O., Hetland, E., Helgerud, J., Hoff, J., & Slordahl, S. A. (2004). High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*, 11(3), 216-222.

- Saxton, J. M., Daley, A., Woodroffe, N., Coleman, R., Powers, H., Mutrie, N., et al. (2006). Study protocol to investigate the effect of a lifestyle intervention on body weight, psychological health status and risk factors associated with disease recurrence in women recovering from breast cancer treatment [ISRCTN08045231]. *BMC Cancer*, 6, 35.
- Schmitz, K. (2011). Physical activity and breast cancer survivorship. *Recent Results Cancer Res*, 186, 189-215.
- Schmitz, K. H., Ahmed, R. L., Hannan, P. J., & Yee, D. (2005). Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev*, 14(7), 1672-1680.
- Schmitz, K. H., Cappola, A. R., Stricker, C. T., Sweeney, C., & Norman, S. A. (2007). The intersection of cancer and aging: establishing the need for breast cancer rehabilitation. *Cancer Epidemiol Biomarkers Prev*, 16(5), 866-872.
- Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., et al. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*, 42(7), 1409-1426.
- Schmitz, K. H., Holtzman, J., Courneya, K. S., Masse, L. C., Duval, S., & Kane, R. (2005). Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 14(7), 1588-1595.

- Schmitz, K. H., Stout, N. L., Andrews, K., Binkley, J. M., & Smith, R. A. (2012). Prospective evaluation of physical rehabilitation needs in breast cancer survivors: a call to action. *Cancer*, 118(8 Suppl), 2187-2190.
- Shan, K., Lincoff, A. M., & Young, J. B. (1996). Anthracycline-induced cardiotoxicity. *Ann Intern Med*, 125(1), 47-58.
- Shapiro, C. L., Hardenbergh, P. H., Gelman, R., Blanks, D., Hauptman, P., Recht, A., et al. (1998). Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. *J Clin Oncol*, 16(11), 3493-3501.
- Shapiro, C. L., & Recht, A. (2001). Side effects of adjuvant treatment of breast cancer. *N Engl J Med*, 344(26), 1997-2008.
- Smith, I. E. (2004). Aromatase inhibitors in early breast cancer therapy. *Semin Oncol*, 31(6 Suppl 12), 9-14.
- Speck, R. M., Courneya, K. S., Masse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*, 4(2), 87-100.
- Sui, X., LaMonte, M. J., & Blair, S. N. (2007). Cardiorespiratory fitness as a predictor of nonfatal cardiovascular events in asymptomatic women and men. *Am J Epidemiol*, 165(12), 1413-1423.
- Tabata, I., Nishimura, K., Kouzaki, M., Hirai, Y., Ogita, F., Miyachi, M., et al. (1996). Effects of moderate-intensity endurance and high-intensity intermittent training on anaerobic capacity and VO₂max. *Med Sci Sports Exerc*, 28(10), 1327-1330.

- Taylor, D. L., Nichols, J. F., Pakiz, B., Bardwell, W. A., Flatt, S. W., & Rock, C. L. (2010). Relationships between cardiorespiratory fitness, physical activity, and psychosocial variables in overweight and obese breast cancer survivors. *Int J Behav Med*, 17(4), 264-270.
- Theuws, J. C., Muller, S. H., Seppenwoolde, Y., Kwa, S. L., Boersma, L. J., Hart, G. A., et al. (1999). Effect of radiotherapy and chemotherapy on pulmonary function after treatment for breast cancer and lymphoma: A follow-up study. *J Clin Oncol*, 17(10), 3091-3100.
- Thomson, C. A., Stopeck, A. T., Bea, J. W., Cussler, E., Nardi, E., Frey, G., et al. (2010). Changes in Body Weight and Metabolic Indexes in Overweight Breast Cancer Survivors Enrolled in a Randomized Trial of Low-Fat vs. Reduced Carbohydrate Diets. *Nutr Cancer*, 62(8), 1142-1152.
- Tjonna, A. E., Lee, S. J., Rognmo, O., Stolen, T. O., Bye, A., Haram, P. M., et al. (2008). Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*, 118(4), 346-354.
- Tolentino, G. P., Battaglini, C. L., Araujo, S. S., Otano, A. S., Conde, D. M., Evans, E. S., et al. (2010). Cardiorespiratory fitness and quality-of-life analysis posttreatment in breast cancer survivors. *J Psychosoc Oncol*, 28(4), 381-398.
- Turner, M. J., Williams, A. B., Williford, A. L., & Cordova, M. L. (2010). A comparison of physiologic and physical discomfort responses between exercise modalities. *J Strength Cond Res*, 24(3), 796-803.

- Vance, V., Mourtzakis, M., McCargar, L., & Hanning, R. (2011). Weight gain in breast cancer survivors: prevalence, pattern and health consequences. *Obes Rev*, 12(4), 282-294.
- Warburton, D. E., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., et al. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am J Cardiol*, 95(9), 1080-1084.
- Wasserman K, Hansen J, & Sue D, e. a. (1999). *Principles of exercise testing and interpretation* (3rd edn. ed.): Lippincott Williams & Wilkins.
- Weesner, K. M., Bledsoe, M., Chauvenet, A., & Wofford, M. (1991). Exercise echocardiography in the detection of anthracycline cardiotoxicity. *Cancer*, 68(2), 435-438.
- Wigmore, D., Fernall, B., Smith, D. (2011). *Advanced Cardiovascular Exercise Physiology (Chapter 9; p: 139-162)*. Champaign: Human Kinetics.
- Winzer, B. M., Whiteman, D. C., Reeves, M. M., & Paratz, J. D. (2011). Physical activity and cancer prevention: a systematic review of clinical trials. *Cancer Causes Control*, 22(6), 811-826.
- Wisloff, U., Stoylen, A., Loennechen, J. P., Bruvold, M., Rognmo, O., Haram, P. M., et al. (2007). Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*, 115(24), 3086-3094.